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2. This Journal accepts Original Papers, Review Articles, Case Reports, Quiz, Short Communications and Letters to the Editor in the fields of clinical dermatology, dermato-pathology, dermatologic surgery and basic sciences related to dermatology.

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5. Photographs / illustrations along with their captions.

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8. Covering Letter

9. Main Manuscript document

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Efficacy of topical 5% imiquimod with cryotherapy versus intralesional meglumine antimoniate in the treatment of anthroponotic cutaneous leishmaniasis

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INTRODUCTION

Cutaneous leishmaniasis (CL) is a major health problem, which is increasing in incidence. Leishmaniasis is endemic in more than 60 countries worldwide. More than 90 percent of CL occurs in Iran, Afghanistan, Syria, Saudi Arabia, Brazil, and Peru. Leishmaniasis is a disease caused by the protozoa of the heterogeneous Leishmania species, transmitted by the bite of a female sandfly and from the sub–family of phlebotominae. CL caused by Leishmania tropica (anthroponotic, ACL in urban areas) or by Leishmania major...
Imiquimod with cryotherapy for treatment of cutaneous leishmaniasis

(zoonotic, ZCL in rural areas) is endemic in Iran\textsuperscript{5,6}. CL initially starts as a papule at the site of a sandfly bite which then increases in size and eventually ulcerates. It may take 3-18 months to heal in over 90\% of cases\textsuperscript{7}. The incubation period lasts from 2 weeks to several months and cases up to 3 years have been reported\textsuperscript{8,9}. CL is a self healing disease, but this can take months or even years\textsuperscript{3}. Treating of CL will accelerate cure and reduce scarring and risk of transmission. This is especially important at cosmically important sites\textsuperscript{10}.

To date, there is no vaccine against leishmaniasis and the available drugs are toxic, expensive and difficult to administer. Moreover, there are evidences of emerging resistance of the parasite to the commonly used drugs. Treatment of CL should be directed towards the eradication of amastigotes and reduction of the size of lesion with minimal scarring and possible toxicity. Several types of treatment regimens have been suggested for CL but until today\textsuperscript{s}, there is no single treatment modality has been indisputably shown to be superior to others\textsuperscript{11}. Options in the treatment of CL include intralalsional injection as pentavalent antimony, hypertonic sodium chloride solution and zinc sulphate; topical treatments as paromomycine ointment, 5\% imiquimod cream, topical amphotericin B; physical therapy as cryotherapy, localized controlled heat, \textsuperscript{12} CO\textsubscript{2} laser, photodynamic therapy; oral treatments as azoles, azithromycin, miltefosine, zinc sulphate and intramuscular or intravenous drugs such as systemic antimonials, pentamidine and amphotericin B.

Imiquimod is an imidazoquinoline amine that has been approved by Food and Drug Administration (FDA) as a 5\% cream for external genital and perianal warts. Imiquimod is an immune response modifier that stimulates innate and adaptive immune pathways, resulting in antiviral, antitumor and immunoregulatory properties. Imiquimod induces cytokine production, most likely via activation of Toll-like receptor 7 (TLR7). Imiquimod is a stimulator of the innate immune response via the induction, synthesis of cytokines, such as IFN, IL6 and TNF\textsuperscript{13}.

Imiquimod demonstrated a leishmanicidal activity by inducing the expression of the inducible nitric oxide synthase (iNOS) gene and the release of nitric oxide\textsuperscript{14}. Imiquimod also stimulates of the Th1 cytokine IFN. Imiquimod is generally well tolerated with the most frequent adverse reactions being mild to moderate inflammation with erythema, erosion, excoriation, flaking and edema\textsuperscript{15}.

In an open study of 12 patients with CL resistant to MA, Imiquimod in combination with MA cured 90\% of the patients\textsuperscript{16}.

In a randomized double-blind clinical trial with use of Imiquimod, a 72 percent cure rate was observed when the cream was used in conjunction with MA in patients with CL who had failed to respond to antimony alone\textsuperscript{17}.

In this study, the efficacy of combination treatment with topical imiquimod cream and cryotherapy was compared with intralesional MA in a randomized, open trial clinical study.

**PATIENTS AND METHOD**

**Participants**

The study was done on patients aged between 5 to 65 years who had CL. The exclusion criteria were: chronic systemic disease such as renal failure, myocarditis, hepatitis and pancreatitis, immune suppression, breast feeding, pregnancy, sporotrichoid and lupoid forms, diameter of lesion >3 cm, disease duration >9 months, number of lesions >2, the past history of sensitization to MA or imiquimod, mucosal lesions and history of receiving other treatment in a recent month.

All the patients with positive smear or skin biopsy with positive Leishman body were enrolled in this study.

Participants, his or her guardian (patients younger than 18 years) were informed about the study and sign of consent form were taken.

**Study setting and location**

The study was carried out in the Kerman province of Iran which is an endemic area for ACL caused by L. tropica\textsuperscript{18}. The eligible patients were recruited among patients with CL who were referred to the Dermatology Clinic and Leishmaniasis research center of Afzalipour Hospital of Kerman, Iran.

**Intervention**

Of 105 patients screened, 75 were entered the
treatment study. Patients were randomly allocated to one of two treatment groups. 39 Patients (24 female and 15 male) were enrolled in group A and 36 patients (21 female and 15 male) in group B (Figure 1).

Group A were treated with combined cryotherapy (biweekly) and 5% imiquimod (Alldara, 3M pharmaceuticals) cream 3 times per week.

Cryotherapy with liquid nitrogen was performed by dipstick technique. It consists of application of a saturated, cotton – tipped applicator on the lesion until 2-3 mm halo forms around it. The freeze time ranges between 10 and 25 seconds. This procedure was repeated every other week.

The patients were also treated with 5% imiquimod cream 3 times per week (Mondays, Wednesdays and Fridays). Imiquimod was provided as 250 mg sachet. A box of sachets was given to each patient, asking them to apply a thin layer of cream on lesions at bedtime, to massage it into the skin thoroughly and wash the lesion 6 to 10 hours after application with soap and water.

Group B patients were treated with intralesional MA weekly (Glucantime, 1.5 gram in 5 cc solution as ampule; Rhodia laboratories, Rhonepoulenc, France). First the lesions were cleaned by povidon iodine. Thirty or 27 gauge needle was used for injection. The solution was injected intradermally in each lesion from all directions until the lesion had completely blanched (0.5 -2cc per lesion per week, depending on the size).

In both groups, the procedure was continued

Figure 1. A total of 50 patients completed follow – up after two types of treatments.
until complete cure or up to 12 consecutive weeks, whichever was earlier. The patients were visited every week after initiation of treatment. Follow-up evaluation was done by clinical assessment of treated lesions every month until 3 months.

Demographic information of the patients, characteristics of the skin lesions (such as induration, ulceration and edema) were registered by special designed observation recording form. The induration size was defined as the greatest diameter of induration of the skin lesion in centimeter that was measured with the collis.

End points

The primary end point of this study was the clinical and laboratory cure of the lesions, defined as complete re-epitelization of 100% (+/-scar), complete flattening of induration and negative smear of the lesions compared with baseline in each visit and also the time of completed cure.

The secondary end points included adverse-effects of two types of treatments and the relapse rate (defined as reappearance of lesions at the site or periphery of previously healed lesions or an increase in the size of lesions after initial improvement) that were assessed at months 1, 2 and 3 after the end of treatment.

The proposal and consent form were reviewed and approved by the ethics committee of the center for research and training of Kerman University of medical sciences.

Statistical analysis

Data, expressed as Mean ± Standard deviation, were analyzed by SPSS software package (version11.5). Chi-square-test and t-test were used for determining the significance of difference between the two groups of treatment. Repeated measure model of ANOVA was used to determine the temporal variation of size of lesion during 12 weeks and the effect of treatment. The difference was considered significant when p<0.05.

RESULTS

A total number of 75 patients with mean age of 15.6±12.2 were entered in the study and 50 (19 male and 31 female) of them (responding rate 88%) completed the follow-up treatment.

The statistic analysis revealed no significant difference in respect to gender, age, location and type of the lesions between two randomized groups (Table 1).

Twenty four patients in group A and 23 patients in group B completed the treatment and had follow-up for twelve weeks. In group A, 16 of 24 patients (65.5%) responded to treatment while in group B, 19 of 23 patients (83.3%) responded to treatment and had complete cure. No difference was observed between two groups (P=0.16) (Table 2).

Repeated measure model of ANOVA showed that temporal variation for size of lesions was significant for both groups (p= 0.000) and no difference was observed in regard to type of treatment (p=0.57) (Figure 2).

Cure rate in week 6 and 12 seemed to be greater in group B; 13.3% (9/25) in group A, 35% (3/25) in group B (Table 2).

<table>
<thead>
<tr>
<th>Group Variable</th>
<th>M.A (N=25)</th>
<th>Imiquimod + Cryotherapy (N=25)</th>
<th>P. Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>61.9%</td>
<td>62.5%</td>
<td>0.59</td>
</tr>
<tr>
<td>Male</td>
<td>38.1%</td>
<td>37.5%</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>71.4%</td>
<td>28.2%</td>
<td>0.04</td>
</tr>
<tr>
<td>Lower limb</td>
<td>4.8%</td>
<td>9.4%</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>23.8%</td>
<td>62.6%</td>
<td></td>
</tr>
<tr>
<td>Type of lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque or ulcerated</td>
<td>57.1%</td>
<td>31.3%</td>
<td>0.056</td>
</tr>
<tr>
<td>Nodule</td>
<td>42.9%</td>
<td>68.8%</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Baseline Demographic and disease characteristics

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>Imiquimod + Cryotherapy</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure rate</td>
<td>0%</td>
<td>0%</td>
<td>0.52</td>
</tr>
<tr>
<td>Mean size of lesion</td>
<td>1.39 ± 0.38</td>
<td>1.76 ± 0.39</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Six</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure rate</td>
<td>35%</td>
<td>13.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean size of lesion</td>
<td>0.60 ± 0.29</td>
<td>0.94 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Twelve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure rate</td>
<td>83.3%</td>
<td>65.5%</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean size of lesion</td>
<td>0.05 ± 0.04</td>
<td>0.33 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Analysis of cure rate between 2 groups based on weeks of follow-up
group B in week 6 and in week 12, 65.5% (16/24) in group A vs. 83.3% (19/23) in group B. But by using Fisher exact test there was no significant difference between two groups in weeks 6 (P=0.09) and 12 (P=0.16) of treatment (Table 2). Three months after the end of treatment, relapse was observed in 2 of 25 patients treated with imiquimod and in 3 of 25 patients treated with MA.

The only adverse effects related to topical treatment were pain and eczematous reaction in 4 patients and local infection in 1 patient treated with imiquimod and they were minimal and most of them were treated by non-steroidal anti-inflammatory drugs (NSAID), topical steroid and topical antibiotic.

DISCUSSION

Although CL is a self-healing disease, it is recommended for patients with ACL to receive treatment because of the prolonged course, potential scar formation and role of infected humans as reservoir 19.

Unfortunately, no ideal therapy for CL is available, and its treatment has remained a challenge. Pentavalent antimonials remain the mainstay of treatment 5. However, a high rate of adverse events, length of treatment, and relapses in up to 25 percent of cases highlight the limitations of these drugs 3.

In this clinical trial, combined imiquimod and cryotherapy was compared with intralesional MA in the treatment of dry type CL.

Imiquimod is an immune response modifier that increases local cytokine production, with a subsequent activation of both the innate (rapid, nonspecific) and adaptive (specific, cellular and humoral) immune systems 20.

In this study, we did not observe significant difference in clinical response between two therapeutic methods (65/5% in group A vs. 83.3% in group B).

In previous study in Iran (Kerman), ninety-nine patients with biopsy-confirmed CL were enrolled in an open label study. After 40 days of treatment, there was a response rate in 23%, 35% and 37% in weekly intralesional MA (n=35), imiquimod (n=29), and combination treatment group of imiquimod 5% cream and intralesional meglumine antimoniate (n=35), respectively, indicating a better response in patients with combination of intralesional MA plus imiquimod cream compared with patients treated with MA 21. In contrast to this study, clinical response in our imiquimod group was higher, 65.5% versus 35%, which this difference may be due to cryotherapy combined with imiquimod.

Miranda et al, recruited 40 patients with clinical resistance to antimony in Peru. All patients received MA (20mg/kg/d intramuscular or intravenous) and were randomized to receive either topical 5% imiquimod cream or placebo as control every other day for 20 days. Lesions resolved more rapidly in the imiquimod group. The cure rate in the imiquimod- treated group was 50% at one month (vs. 15% in the placebo group), 61% at 2 months (vs. 25%), and 72% at 3 months (vs. 35%) (P<0.05 at all time points) 17. This study was performed in some parts of Peru, that were endemic for the new world CL, but our study was conducted in an endemic area of old world CL caused by L. tropica. All patients in the Miranda study, previously has been treated with MA (intramuscular or intravenous), but none of the patients in our study were treated previously with MA.

In a study in Mashhad (Iran), Firooz et al treated 59 patients with Imiquimod and intramuscular MA (20 mg/kg of pentavalent antimony daily for 2 weeks) and the control group was treated with placebo and intramuscular MA. This study revealed no beneficial effect of combining a 4 week course of treatment with 5% imiquimod cream and a standard course of treatment with MA in patients with CL in an endemic area of L. tropica 19.

In Firooz et al study, patients were treated with combined MA (intramuscular) and imiquimod, but in our study patients were treated with imiquimod and cryotherapy and in control group patients
received MA intralesionally. This may be explained the diversity of responses between two studies.

Our results thus demonstrated that topical application of imiquimod with cryotherapy has the less significant effect in comparison with MA alone for the treatment of Old World CL. This therapy may have particular advantages for cases with facial lesions and for children, because intralosomal injection with pentavalent antimony is a relatively painful procedure which needs to be performed regularly every 1-2 weeks, but imiquimod is well tolerated.

Clinical trials for CL are usually confronted due to differences in the design, duration of treatment, sample size, end point definition, causative organisms, etc. It seems that combination therapy has important place for treatment of CL. Imiquimod can be one of this combination because of immunomodifying effect in regard to pathogenesis of CL. Further studies are needed to evaluate this effect.

REFERENCES

The effect of different concentrations of topical podophyllin on cutaneous leishmaniasis

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INTRODUCTION

Leishmaniasis is an infectious disease¹ commonly caused by different kinds of leishmania like leishmania tropica (in urban areas) and leishmania major (in rural areas) in the old world. The phlebotomine insect vector bite transmits leishmaniasis to humans².

Leishmaniasis is characterized by a clinical, immunological and histopathological range that is associated with immunological capability of the host, the species and virulence of the parasite and inadequately defined environmental factors. Clinical manifestations of leishmaniasis are cutaneous, mucosal and visceral lesions. A rare form is diffuse cutaneous leishmaniasis (DCL) that is related to the imperfect cell-mediated immune response to the leishmania parasite³.

The first line treatment for Leishmaniasis is still pentavalent antimonials, but other drugs such as amphotericin B, paromomycin, imidazoquinoline derivatives, and miltefosine have been studied in other reviews for treatment of leishmaniasis⁴⁵.

Although many treatment modalities are present, there is no perfect therapy for leishmaniasis.
Some treatments such as glucantime are painful and costly, other treatments have side effects such as headache, vomiting, skin reaction and abdominal pain. As a result, development of more efficient and easily tolerated medications that can be suitably administered are of important advantages. Podophyllin is a plant alkaloid used for the treatment of genital warts. It interferes with cell replication, crosses cell membranes and works as a keratolytic that causes arrest of cell mitosis in metaphase.

In this study, we postulated podophyllin could eradicate *leishmania* parasite by arresting cell mitosis; therefore, we used different concentrations of podophyllin in vitro on *leishmania* parasites and then on leishmaniasis lesions in mice and compared their efficacy.

**MATERIAL AND METHODS:**

**Cell culture**

*Leishmania major* (MRHO/IR/75/ER) promastigotes were cultured at 26°C in RPMI 1640 containing 10% fetal calf serum (FCS) and antibiotics. The log-phase promastigotes were washed in phosphate-buffered saline (PBS), adjusted to a concentration of 1 x 10^6 cell/ml into 96 wells plate in a fresh medium. Podophyllin was added to the promastigotes (14.3 μg /ml). After incubation at 26°C for 1h, 2h and 24 h at 5% CO₂, the promastigotes were counted and checked for viability using a light microscope.

**Mouse infection**

Fifty four BALB/c mice (4- to 6-week-old female) were purchased from Pasteur Institute, Karaj, Iran. The animal experiments were carried out according to Ethical Committee Acts of the Shahid Beheshti and Tehran University of Medical Sciences. Mice were inoculated subcutaneously at the base with amastigote forms obtained from the spleen and the liver of mice infected with *leishmania major* (MRHO/IR/75/ER). Four groups were tested by podophyllin 5%, podophyllin 10%, podophyllin 20% and control group (infected but untreated mice). Podophyllin was applied using a sterile tip directly onto the skin to form a thin layer once weekly for 4 weeks. The treated area was then left open without dressing. Images were taken at baseline and then weekly. The lesion size measurement (mm) was done weekly with a caliper. Ethical committee of the Skin Research Center of Shahid Beheshti Medical University approved the study protocol in March 2009 (Certificate number: 1112MTB).

**Statistical analysis**

The Kruskal-Wallis test was used to compare groups at similar sessions and in case of any difference, the Mann-Whitney-U-test with Bonferroni correction was applied for pair-wise comparisons. For each group, Friedman test was used to evaluate the differences of lesions’ diameters among the five time-points (baseline, and after 1, 2, 3 and 4 weeks) and if there were any differences, the Wilcoxon tests with Bonferroni corrections were conducted to compare the lesions’ diameters at each week with the previous week and baseline. Statistical analysis was performed using the statistical software SPSS 16 (SPSS Inc. Chicago, IL, U.S.A.). P values less than 0.05 were considered significant.

**RESULT**

Podophyllin, 14.3 μg /ml used in vitro, eradicated *leishmania major* parasites. The first group (13 mice), second group (13 mice) and third group (12 mice) were treated with podophyllin 5%, 10% and 20% respectively. The control group (13 mice) did not receive any treatment.

The four groups were compared according to lesions’ diameters at similar sessions. There were no statistical significant differences in lesions’ diameter among the groups at baseline (p=0.105).

At first week, a significant difference in lesions’ diameter was observed in all groups (p=0.004) and pair-wise comparisons showed a significant difference between podophyllin 10% and the control group, and between podophyllin 20% and the control group (p=0.006 and p<0.001, respectively). Mean lesions’ diameter of the podophyllin 10% and 20% groups were more than control group one week after beginning of the treatment (Table 1).

At second week, there was a significant difference in lesions’ size among four groups (p<0.001) and with pair-wise comparisons, significant differences between podophyllin 10% and the
control group, podophyllin 20% and the control group, and between podophyllin 5% and 10% groups were demonstrated (p=0.001, p=0.005 and p=0.002, respectively). According to Table 1, the mean lesions’ diameter at the second week after beginning of the treatment in podophyllin 10% group was more than podophyllin 5% and the control group.

At weeks 3 and 4, no significant difference was observed among four groups (Table 1). There were significant increases in lesions’ diameters of control group at second week in comparison to first week and at third and fourth weeks in comparison to baseline (p=0.005, p=0.001 and p=0.002, respectively) (Figure 1).

In the podophyllin 5% group, there were significant increases in lesions’ diameter at the second and fourth week in comparison with the baseline and also at fourth week in comparison with the third week (p=0.004, p=0.002 and p=0.002, respectively) (Figure 1).

Significant increases in lesions’ diameters of second, third and fourth weeks in comparison with baseline and of second week in comparison to first week were observed in podophyllin 10% group (p-values at most 0.004) (Figure 1).

Finally, there were significant increases in lesions’ diameter of the podophyllin 20% group at the first, second, third and fourth weeks in comparison with baseline, and the fourth week compared to the third week (p-values at most 0.005) (Figure 1).

**DISCUSSION**

Leishmaniasis has a big range of clinico-pathological forms and therefore needs different treatments. The most common type of cutaneous leishmaniasis (CL) treatment is antimonials. Intralesional injection of antimonials can prevent side-effects resulting from systemic administration 7 and numerous studies have confirmed their efficacy in the treatment of CL 8-12. Various other drugs have also been used but all have limitations concerning ease of use and financial aspects 4,5.

Podophyllin is a plant alkaloid 6, commonly used in topical forms such as a chemotherapeutic agent 13. It interferes with cell replication, crosses cell membranes and works as a keratolytic that causes arrest of cell mitosis in metaphase 6. Podophyllin has been applied in many disease e.g oral hairy leukoplakia 14-16, measles and herpes simplex virus type I infection 17, condyloma acuminatum 18,19, cytomegalovirus and Sindbis virus infections 20. Also, it has an anti-tumor and anti-rheumatoid arthritis activity 21 and has been traditionally used for the treatment of genital warts 6.

Despite the evident beneficial effects of podophyllin, no study has been conducted to assess its effects on leishmaniasis. In this regard, in the present study, the efficacy of podophyllin was investigated on leishmaniasis. The present survey postulated that podophyllin could eradicate *leishmania* parasite by arresting cell mitosis. Therefore, we used different concentrations of podopoyllin in vitro on *leishmania* parasites and then on leishmaniasis lesions in mice and compared their efficacy.

Our study demonstrated that podophyllin could eradicate *leishmania* parasite in vitro although in mice, after four weeks of treatment, the mean lesion size increased significantly in podophyllin groups with different concentrations and also in the

### Table 1. Mean (standard deviation) diameters of lesions by groups over time.

<table>
<thead>
<tr>
<th>Group</th>
<th>baseline (mean, SD)</th>
<th>1th week (mean, SD)</th>
<th>2th week (mean, SD)</th>
<th>3th week (mean, SD)</th>
<th>4th week (mean, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podophyllin 5%</td>
<td>4.74 (1.87)</td>
<td>6.19 (1.93)</td>
<td>7.64 (1.73)</td>
<td>7.04 (3.29)</td>
<td>10.10 (2.57)</td>
</tr>
<tr>
<td>Podophyllin 10%</td>
<td>4.65 (0.98)</td>
<td>6.78 (1.58)</td>
<td>10.57 (3.02)</td>
<td>8.03 (3.10)</td>
<td>9.42 (3.73)</td>
</tr>
<tr>
<td>Podophyllin 20%</td>
<td>4.56 (1.79)</td>
<td>7.15 (1.34)</td>
<td>8.92 (1.32)</td>
<td>9.28 (1.79)</td>
<td>11.01 (2.26)</td>
</tr>
<tr>
<td>Control</td>
<td>5.72 (2.46)</td>
<td>5.21 (1.06)</td>
<td>6.96 (1.84)</td>
<td>8.80 (2.13)</td>
<td>10.08 (2.27)</td>
</tr>
</tbody>
</table>

**Figure 1.** Mean diameters of lesions by groups over time.
The effect of topical podophyllin on cutaneous leishmaniasis

control group over time. Our findings suggested that podophyllin was not an appropriate drug for the treatment of CL. A possible explanation could be the anti mitotic effect of podophyllin, which prevents the proliferation of cells near the lesion thus resulting in the expansion of the wound. This effect was more prominent especially when we used podophyllin 20%.

The reason we did not achieve proper results from our study may refer to the fact that the dose of podophyllin was not adjusted appropriately according to the weight of the mice, which led to disorganization in cellular proliferation. Another limitation of our study was that we did not check the parasite burden by smear from the lesions, and podophyllin might have been injected into a non-healing ulcer without any parasites in some cases. In conclusion, treatment with different doses of podophyllin could not accelerate the healing process of leishmaniasis lesions. However, further structured studies could be more beneficial to elucidate the possible role of podophyllin in the treatment of cutaneous leishmaniasis.

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Clinical efficacy and tolerability of valacyclovir versus acyclovir in treatment of herpes zoster

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INTRODUCTION

Herpes zoster remains an important medical problem throughout the world. It may occur at any age in the otherwise immunocompetent individuals. The reported incidence in the general population ranges from 0.8 to 4.8 per 1000 persons \textsuperscript{1}. The characteristic rash and associated pain may occur when varicella zoster, which becomes dormant in sensory ganglia following primary varicella zoster virus infection, is reactivated, often in association with declining cellular immunity associated with advancing age \textsuperscript{2}. Post herpetic neuralgia is one of the most common complications of herpes zoster. The incidence of post herpetic neuralgia varies with age. It is rare under 40 years but about 50%
Efficacy and tolerability of valacyclovir in treatment of herpes zoster

Acute herpes zoster presents with skin rashes distributed over one or more dermatomes that usually resolve within 4 weeks; however, in an untreated patient, the associated pain and postherpetic neuralgia, may persist for several months to even years and can be a serious disabling condition, particularly in the elderly. Replication of varicella zoster virus in the ganglion of involved nerve results in destructive inflammation and/or nerve dysfunction. This may partly explain the pain, although the full pathogenesis of the syndrome is not clear.

Oral Acyclovir (800mg five times daily) is widely used for the treatment of acute herpes zoster. It speeds rash healing and decreases the severity of acute pain. In some studies, acyclovir also appears to reduce the prevalence, severity and duration of chronic pain. The limited oral bioavailability of acyclovir, however, necessitates frequent dosing to achieve a better therapeutic concentration in plasma for the treatment of acute herpes zoster.

Valacyclovir, 2-[2-amino-1, 6-dihydro-6-oxo-9H-purin-9-yl-methoxy] ethyl valinate hydrochloride, is the L-valine ester of acyclovir. It was developed to provide increased oral bioavailability of acyclovir. Valacyclovir is better absorbed than acyclovir due to an active stereoselective transporter in intestinal brush border membrane. Valacyclovir is converted rapidly and virtually to acyclovir after oral administration in healthy adults by intestinal and hepatic first pass metabolism through hydrolysis. Thus, the mechanism of action and spectrum of activity of valacyclovir are the same as that of acyclovir. Unlike acyclovir, valacyclovir is a substrate for intestinal and renal peptide transporters. Therefore, the proportion of bioavailability of acyclovir increases 3-5 times greater to approximately 70% following valacyclovir administration. The comparatively better oral bioavailability of valacyclovir contributes to the need for less frequent administration. Apart from the differences in bioavailability, the mechanism, clinical spectrum and adverse effects are similar.

This randomized prospective study was conducted in Midnapore Medical College and Hospital to assess the clinical efficacy, safety and tolerability of oral valacyclovir versus standard oral acyclovir in the treatment of herpes zoster.

**PATIENTS AND METHODS**

This randomized prospective study of valacyclovir versus acyclovir for the treatment of acute herpes zoster was carried out in Midnapore Medical College and Hospital between March 2007 and August 2007.

**Patients**

Non-pregnant patients who were 40 years of age or older, were immunocompetent and were not on any immunosuppressive medication and presented within 72 hours after the onset of rash were enrolled in the study. The clinical diagnosis of herpes zoster was based on the presence of unilateral dermatomal rash. The ethics committee of Midnapore Medical College and Hospital approved the study protocol. A written informed consent was obtained from each patient prior to enrollment. Routine hematological examination, liver function test and renal function test (urea and creatinine) were done before the treatment and after completion of valacyclovir/acyclovir therapy.

**Drug administration**

A total of sixty patients were included in the study. Out of them, 30 patients were treated with valacyclovir and remaining 30 patients with acyclovir. The patients were selected randomly, those with even number were put on valacyclovir and the odd ones were given acyclovir. Thus, the patients were randomized to receive either 1000 mg valacyclovir three times daily from the day of presentation for 7 days or oral acyclovir 800 mg five times daily for the same period.

**Efficacy assessment**

At the time of presentation, the patients were evaluated for zoster rashes including the proportion of the total lesion area consisting of macules/papules, vesicles, crusts and healed rashes, the distribution of rash (trigeminal, cervical, thoracic and lumbar sacral) and prodromal symptoms. The patients were reviewed after 1 week (8th day), 2 weeks (15th day) and 4 weeks (29th day) to assess response to treatment in both groups. The responses were evaluated by the percentage of improvement...
in skin lesion and zoster associated pain in each visit and the appearance of post herpetic neuralgia after the 4th week.

The impact of pain on daily activities was determined using a numerical scale with six levels as follows: 0 = no pain and discomfort, 1 = Pain can easily be ignored, 2 = Pain does not interfere with daily activities, 3 = pain interfered with concentration or sleep, 4 = Pain interfered with all but basic needs, 5 = Pain required rest or bed rest.

All adverse effects were recorded during the follow-up period.

Statistical analysis

Student t-test, odds ratio (OR) and 95% confidence interval (CI) was calculated following standard statistical method. The differences in the severity of zoster associated pain, skin rash and presence of post herpetic neuralgia between the two treatment groups was compared using chi-square test. All statistical tests were done using EPI6 statistical package. A p-value less than 0.05 was considered significant.

RESULT

A total of 60 patients with herpes zoster were enrolled in the study. They were randomized into two groups- valacyclovir (n = 30) and acyclovir (n = 30). All the patients completed the 4-week study period and were reviewed after one week, two weeks and four weeks. None of these patients withdrew because of serious adverse events. Only one patient on valacyclovir and two patients on acyclovir complained of nausea and mild abdominal pain, but they continued the treatment. More importantly, no abnormalities were detected during the routine hematological, liver or renal function tests either before or after treatment.

Of 60 patients, 40 (66.7%) were male and 20 (33.3%) were female. The mean age of the patients was 51.9 ± 8.9 years; no significant difference was observed between two treatment groups. Moreover, there were no significant differences between two groups in other basic characteristics. There were four types of herpes zoster patients in this study; among them thoracic type is the commonest (56.6%). Other types are cervical (28.3%), trigeminal (10%) and lumbosacral (5%). Most of the patients (60.0%) complained of prodromal symptoms (Table 1).

During the 1st review period (i.e. the 8th day), we noticed that most of the patients improved partially. We accepted the 75% skin lesion improvement as the significant improvement on the 8th day of treatment. By the 15th day, most of the patients showed complete healing of the skin lesions. Hence, on the 15th day, we accepted 100% improvement as the significant improvement (Figure 1,2).

The changes in skin lesions following the treatment are presented in Table 2. Faster resolution of skin lesions was noted in the valacyclovir group compared to acyclovir group during the 1st review (the 8th day) (90.0% vs. 20.0%) and the 2nd review (15th day) (93.3% vs. 30%) and the comparison was statistically significant (p<0.001). After the 4th week, skin lesions healed completely in all the patients of both groups.

Table 3 presents the rate of zoster-associated pain after treatment. At 8th day, zoster associated

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Total patients</th>
<th>Acyclovir</th>
<th>Valacyclovir</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year) Mean ± SD</td>
<td>51.9 ± 8.9</td>
<td>50.7 ± 8.7</td>
<td>53.2 ± 8.9</td>
<td>0.276</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (66.6%)</td>
<td>19 (63.3%)</td>
<td>21 (70.0 %)</td>
<td>0.782</td>
</tr>
<tr>
<td>Female</td>
<td>20 (33.4%)</td>
<td>11 (36.7%)</td>
<td>9 (30.0%)</td>
<td>0.782</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>34 (56.6 %)</td>
<td>17 (56.7 %)</td>
<td>17 (56.7 %)</td>
<td>0.794</td>
</tr>
<tr>
<td>Cervical</td>
<td>17 (28.3%)</td>
<td>9 (30 %)</td>
<td>8 (26.7 %)</td>
<td>0.998</td>
</tr>
<tr>
<td>Trigeminal</td>
<td>6 (10.0 %)</td>
<td>2 (6.7%)</td>
<td>4 (13.3%)</td>
<td>0.673</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>3 (5.0%)</td>
<td>2 (6.7%)</td>
<td>1 (3.3%)</td>
<td>0.991</td>
</tr>
<tr>
<td>Presence of Prodomal symptom</td>
<td>36 (60.0%)</td>
<td>19 (63.3%)</td>
<td>17 (56.7 %)</td>
<td>0.796</td>
</tr>
</tbody>
</table>
Efficacy and tolerability of valacyclovir in treatment of herpes zoster

It was observed that the presence of post herpetic neuralgia was more common in the valacyclovir group than the acyclovir group but with no significant difference (83.3 % vs 70.0%, p>0.05).

**DISCUSSION**

The 4-week randomized parallel and controlled study demonstrated that treatment with valacyclovir three times daily was effective in treating patients with herpes zoster. Overall, women may have a slightly greater risk of developing zoster when compared to men; but in the present study, we observed that men were more frequently affected than women (66.6% vs. 33.4%)\(^\text{15}\). This study showed that the commonest type of herpes zoster pain was less in the valacyclovir group compared to the acyclovir group (56.7% vs. 36.7%) but the differences was not statistically significant. However, at 15\(^\text{th}\) day, 83.3% of the patients in the valacyclovir group reported no pain compared to 40.0% of patients in the acyclovir group, and the differences was highly significant (P<0.001). Table 4 shows the incidence of post herpetic neuralgia in both treatment groups as evaluated after 28 days. It was observed that the presence of post herpetic neuralgia was more common in the valacyclovir group than the acyclovir group but with no significant difference (83.3 % vs 70.0%, p>0.05).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** (a) Herpes zoster lesion before treatment with acyclovir. (b) Clinical improvement after 7 days of treatment with acyclovir.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** (a) Herpes zoster lesion before treatment with valacyclovir. (b) Clinical improvement after 7 days of treatment with valacyclovir.

<table>
<thead>
<tr>
<th>Days</th>
<th>In Acyclovir Group (n =30)</th>
<th>In Valacyclovir Group (n =30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8(^\text{th}) day (75% reduction)</td>
<td>6 (20.0%)</td>
<td>27 (90.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15(^\text{th}) Day (100% reduction)</td>
<td>9 (30.0%)</td>
<td>28 (93.3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2.** Comparison of skin changes of herpes zoster in patients treated with acyclovir versus valacyclovir

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was thoracic (56.6%) as mentioned in previous studies. The prodromal symptoms commonly preceded the herpes zoster eruption (60%) similar to other studies.

Skin lesions improved faster in patients on valacyclovir compared to acyclovir (93.3% vs. 30.0%) and the difference was statistically significant. An earlier study also noticed the faster resolution of skin lesion in valacyclovir group but their findings were not statistically significant. Pain is the most common debilitating feature of herpes zoster. The majority of the patients experience pain immediately before and during the acute rash phase. However, a more important clinical concern is to prevent or reduce the possibility of persistent pain. A significant improvement in zoster-associated pain was noticed in the present study in patients on valacyclovir compared to acyclovir (83.3% vs. 40.0%) unlike other studies.

Post herpetic neuralgia was more frequently seen in patients who were on valacyclovir rather than acyclovir (83.3% vs. 70.0%) but the difference was not statistically significant. However, a large multicentre study found that the treatment with valacyclovir for 7 days significantly reduced the incidence of the post herpetic neuralgia compared to acyclovir.

A recent review documented that valacyclovir significantly decreased the incidence and severity of post herpetic neuralgia. Valacyclovir recipients had a mean duration of 40 days of pain after lesion resolution compared to 60 days of pain after lesion resolution for acyclovir recipients. In terms of zoster-related discomfort, it is estimated that valacyclovir provides a 25% benefit over acyclovir. In our study, we also found that skin lesions and zoster-associated pain improved significantly faster in the valacyclovir group while we noted no significant reduction in post herpetic neuralgia. The less frequent dosing schedule of valacyclovir is mainly due to its enhanced bioavailability of 65% compared to 15% to 20% for acyclovir which allows for more convenient dosing adjustment.

Safety profile of acyclovir has been carefully established during more than 18 years of clinical use. In the present study, there was no clinically significant difference in nature, frequency or severity of adverse events between the two treatment groups, as reported in earlier studies.

In conclusion, our study demonstrated that administration of valacyclovir three times daily was an effective and safe treatment for acute herpes zoster. Treatment with valacyclovir has the benefits of rapid resolution of skin lesions and zoster-associated pain compared to acyclovir, but no additional benefit was noted in the incidence of post herpetic neuralgia. Valacyclovir has the convenience of a three times daily dosing, thereby ensuring better patient compliance, which makes this regimen an excellent choice for treatment of herpes zoster. However, studies on larger numbers of patients are required to assess the incidence of post herpetic neuralgia in treatment with valacyclovir and acyclovir and elucidate the cost effectiveness of valacyclovir versus acyclovir in different societies.

Acknowledgement

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Table 3. Comparative efficacy in improving zoster associated pain.

<table>
<thead>
<tr>
<th>Days</th>
<th>In Acyclovir Group (n =30)</th>
<th>In Valacyclovir Group (n =30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8th day (75% improvement)</td>
<td>11 (36.7%)</td>
<td>17 (56.7%)</td>
<td>0.196</td>
</tr>
<tr>
<td>15th Day (No pain)</td>
<td>12 (40.0%)</td>
<td>25 (83.3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4. Incidence of post herpetic neuralgia.

<table>
<thead>
<tr>
<th>Days</th>
<th>In Acyclovir Group (n =30)</th>
<th>In Valacyclovir Group (n =30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>29th day</td>
<td>21 (70.0%)</td>
<td>25 (83.3%)</td>
<td>0.222</td>
</tr>
</tbody>
</table>


308-nm excimer laser plus topical calcipotriol in the treatment of vitiligo; A single blind randomized clinical study

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INTRODUCTION

Vitiligo is a worldwide disease with a prevalence of about 1-3%. There is a large variety of therapeutic agents, but its treatment still remains a challenge ¹⁻⁴. There is no consensus regarding its etiology, but there are different hypotheses for its pathogenesis such as cellular autoimmunity, oxidative stress, melanocytorrhagy, heredity and neural factors. Based on the supposed etiologies, different treatment options have been tried and approved, meaning that molecular and cellular mechanisms hold the key for various therapeutic agents used. A better understanding of vitiligo repigmentation provides new alternatives and enhances the efficacy of current treatments ⁵.

Phototherapy including PUVA, broad band UVB, narrow band UVB (the preferred form of phototherapy for the treatment of vitiligo) and 308-nm excimer laser (emit focused wavelength...
adjacent to NBUVB 311-nm) are immunomodulator agents and stimulators of the melanocyte precursors; therefore, they are proper options for the treatment of vitiligo. Based on the etiopathomechanisms of vitiligo, adjunctive agents combined with phototherapy, with the purpose of efficacy enhancement and minimizing their long-term side effects such as carcinogenicity, have been suggested. Calcipotriol, which is a synthetic analog of vitamin D₃, is one of them. It causes proliferation, activation and migration of melanocytes as well as modifying T-cell activation. At the molecular level, combination of calcipotriol with different forms of phototherapy and 308-nm excimer laser can decrease lesion progression in vitiligo by immunosuppression, and possibly induce repigmentation by activating melanocyte precursors and melanogenic pathways synergistically. There are some studies which have shown enhancement of PUVA and NBUVB efficacy when calcipotriol was added, but no improvement has been reported in outcomes in other studies. To our knowledge, there is only one report in the literature; this report failed to show the synergistic effect of the combination of calcipotriol and 308 nm excimer laser in the treatment of vitiligo. To date, it has been impossible to explain the contrast between the convincing results of molecular research and the results of such clinical studies, thus, the necessity of precise clinical studies is felt to explain such differences and find more efficient therapies. Therefore, we decided to determine whether calcipotriol could enhance the efficacy of 308nm excimer laser in the treatment of vitiligo in a randomized clinical trial.

**PATIENTS AND METHODS**

**Patients**

This randomized, controlled, prospective, right/left comparative and single blinded clinical trial study was done in the laser clinic of Behsima Center, Tehran, Iran, between May 2007 and May 2009. Inclusion criteria were generalized vitiligo for at least one year or stable vitiligo in all skin color phenotypes. Exclusion criterion were pregnancy, lactation, allergy to calcipotriol, renal insufficiency, abnormality of bone or calcium metabolism, light-sensitive dermatoses, photodermatoses, phototoxic systemic or topical medication(s), previous history of arsenic exposure, excessive exposure to UV light and previous history of skin cancer.

The study was approved by the Ethics Committee under the supervision of vice-chancellor for Research of Tehran University of Medical Sciences. Treatment approach, duration of treatment and possible complications were explained to the patients. All patients signed the informed consent form.

**Treatment protocol**

Included patients with symmetrical vitiliginous lesions were randomized into 2 groups. The intervention group received 308-nm excimer laser plus Calcipotriol ointment 0.005% (Daivonex®) on the lesions of the right side of the body and the control group received 308 nm excimer laser plus vaselin on the lesions of the right side. All patients in both groups administered vaselin on the lesions of the left side. Excimer laser was used two times weekly for 12 weeks. The average initial dose was 50 mJ/cm². The incremental dose was 50 mJ/cm² at each exposure. If there were moderate to severe erythema, irritation or itching, therapy was suspended until the complication was resolved; then, the dose of the laser decreased by 20% of the last session dose. If severe and non resolving complications happened, that patient left the study and received proper treatment prescribed by a dermatologist. Calcipotriol ointment 0.005% (Daivonex®) and vaselin were used 2 times daily.

**Efficacy assessments**

The evaluation of the patients was performed at baseline and at 12th week (the last laser session). At each evaluation, all lesions were photographed and visual scale software was used for comparing the diameter of the lesions before and after treatment in each group. Also, response rate (percentage of repigmentation) was scored (Table 1).

<table>
<thead>
<tr>
<th>Repigmentation Rate (%RR)</th>
<th>Response interpretation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR ≤1</td>
<td>No response</td>
<td>0</td>
</tr>
<tr>
<td>1 &lt; RR ≤25</td>
<td>Mild response</td>
<td>1</td>
</tr>
<tr>
<td>25 &lt; RR ≤50</td>
<td>Moderate response</td>
<td>2</td>
</tr>
<tr>
<td>50 &lt; RR ≤75</td>
<td>Good response</td>
<td>3</td>
</tr>
<tr>
<td>75 &lt; RR ≤100</td>
<td>Excellent response</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1. Repigmentation rate and response score
The score of repigmentation and the side effects in each evaluation were documented in pre-designed forms for each patient.

**Statistical analysis**

SPSS version 15.0 package software was used for statistical analysis. Outcomes of groups were compared with T test. P-values< 0.05 were considered statistically significant.

**RESULTS**

A total of 83 patients (42 females and 41 males) with bilateral symmetrical vitiliginous lesions were included in this study in a period of 2 years, from May 2007 to May 2009. Among them, 13 patients did not complete the study for unknown reasons. Seventy patients, 36 females (51.43 %) and 34 males (48.57%), completed the study. All patients were divided into 2 groups, intervention group (35 patients) and control group (35 patients) through blocked randomization (Figure 1). Baseline demographic and clinical characteristics of each group are detailed in Table 2.

The number of the patients with the response rate scores of 0 (no response), 1 (mild), 2 (moderate), 3 (good) and 4 (excellent) was 1 (2.8%), 3 (8.5%), 19 (54.2%), 10 (28.5%) and 2 (5.7%) in the intervention group and 3 (8.5%), 4 (11%), 16 (45.7%), 9 (25.7%) and 3 (8.5%) in the control group (right side lesions), respectively (Figure 2).

In other words, 31 patients in the intervention group (308 nm excimer laser + calcipotriol) and 28 patients in the control group (308 nm excimer laser + vaselin) were clinical responders (scores 2,3,4). The details of the clinical response rates of right side lesions of each group, considering sex,
duration of disease, skin phenotype and anatomical location, are shown in Table 3.

As Table 3 shows, sex, duration of disease, skin phenotype and anatomical location of right side lesions did not affect the number of clinical responders (scores 2,3,4) in 2 groups significantly.

Spontaneous resolving of lesions was considered as a confounding factor, and for determining its effect, diameter changes of left side lesions that only received vaselin were evaluated in both groups; the changes were from 27.28 cm² to 26.40 cm² in the intervention group and from 26.45 cm² to 26.45 cm² in the control group but the differences were not significant in each group (p-value=0.95 in the intervention group and p-value=1.00 in the control group). The diameter of the right side lesions in the intervention group (308nm excimer laser + calcipotriol) and the control group changed from 27.86 cm² to 16.02 cm² and from 27.21 cm² to 15.82 cm², respectively. The diameter changes were statistically significant in each group (p-value<0.001).

The adverse reactions were erythema and pruritus; all were mild. There were no significant differences in side effects between 2 groups. No patient left the study due to side effects.

For determining the main goal of this study, diameter changes of right side lesions in the intervention group (308nm excimer laser + Calcipotriol), 11.84 cm², was compared to the control group (308nm excimer laser + vaselin), 11.39 cm², but the difference was not significant (p-value=0.74).

**DISCUSSION**

Despite various therapeutic agents for vitiligo, its treatment still remains unsatisfactory. To date, one of the most established treatments is NBVUB. The slow response of vitiliginous lesions on one hand and worsening of their appearance initially, when treated with NBVUB due to tanning of the surrounding skin on the other, have encouraged dermatologists to use a focused and high dose light (308-nm excimer laser) on the affected skin and try different combinations to find a synergistic effect with the purpose of avoiding photodamaging of
the unaffected skin and achieving the response more rapidly. Despite the small skin carcinogenicity risk of any UVB therapy, the real risk of excimer laser still remains unknown, so caution should be taken. Considering molecular mechanisms, different combinations with phototherapy (PUVA, NBUVB, and excimer Laser) have been tried in the treatment of vitiligo 6-11. While Sassi et al, showed the efficacy of topical hydrocortisone 17-butyrate cream in enhancing the effect of excimer laser in the treatment of vitiligo of the face and neck 12 and Kawalek et al, showed the efficacy of topical tacrolimus plus excimer laser 13, others decided to try the combination of calcipotriol with phototherapy. Goldinger et al, 2007, in a non randomized single blind study containing 10 patients, showed that calcipotriol 2 times daily did not enhance the efficacy of excimer laser (3 times weekly) in the treatment of vitiligo. According to our study, calcipotriol did not enhance the efficacy of excimer laser in the treatment of vitiligo. This conclusion was achieved according to diameter changes in intervention and control group lesions and removing the effects of the confounding factors, although not significant.

However, we may have reached this conclusion because we used 308 nm excimer laser plus calcipotriol schedule, our timing or our preparation; therefore, different types of regimen schedules should be tried to determine the real effect of vitamin D derivatives on enhancing excimer laser efficacy in the treatment of vitiligo. To our knowledge, this was the first phase 2 randomized clinical trials done to investigate whether topical calcipotriol enhances 308-nm excimer laser efficacy in the treatment of vitiligo. In conclusion, our study showed that combination of excimer Laser with calcipotriol did not produce a superior result in the treatment of vitiligo than did excimer laser alone.

REFERENCES


<table>
<thead>
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<th>Table 3. Treatment outcome</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Duration of disease</td>
</tr>
<tr>
<td>1-2 years</td>
</tr>
<tr>
<td>3-5 years</td>
</tr>
<tr>
<td>&gt;5 years</td>
</tr>
<tr>
<td>Skin phenotype</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Anatomical location</td>
</tr>
<tr>
<td>Head &amp; neck</td>
</tr>
<tr>
<td>Trunk</td>
</tr>
<tr>
<td>Upper limb (proximal)</td>
</tr>
<tr>
<td>Upper limb (distal)</td>
</tr>
<tr>
<td>Lower limb (proximal)</td>
</tr>
<tr>
<td>Lower limb (distal)</td>
</tr>
</tbody>
</table>

*Clinical responders No. (score2, 3, 4)
Excimer laser plus topical calcipotriol in the treatment of vitiligo


Erythroderma in Khuzestan province, southwest of Iran

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Conflict of interest: None to declare

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INTRODUCTION

Erythroderma, also known of exfoliative dermatitis and first described by Herba in 1868 1, is a reaction pattern characterized by generalized or nearly generalized and confluent erythema affecting more than 90% of the body surface and accompanied by a variable degree of scaling. Due to the large areas of the affected skin and the advanced age of most patients, erythroderma imposes an important risk to the life of the patients 2. A variety of diseases and other exogenous factors may cause this condition. Therefore, it is important to identify and treat any underlying disease whenever possible and to remove any contributing external factors 3. The aim of our study was to assess the frequency of different etiologies, the sex ratio and the age of the patients at the onset of erythroderma.

PATIENTS AND METHODS

Because erythroderma imposes an important risk to the life of the patients, we generally treat them as inpatients. In a retrospective study, we...
reviewed the files of 85 patients diagnosed with erythroderma out of 6210 patients who were admitted to the dermatology ward of Sina Hospital affiliated to Jundishapur Medical University of Ahvaz in a period of about 9 years from 1980 to 1989. We studied the medical records of all erythrodermic patients by checking the data of clinical and pathologic reports and the final etiologic diagnosis. All data were tabulated for further analysis.

**RESULTS**

In the above-mentioned period, the total number of admissions was 6210 patients of whom 85 patients were erythrodermic. The frequency of erythroderma in our dermatology department was 1.37%. Regarding the 3.5 million population of Khuzestan province and the 9-year period of this study, the incidence of erythroderma in Khuzestan province was estimated about 0.27 per 100,000 inhabitants per year. The sex ratio (male/female) was 1.6:1. The mean age of our patients was 49.11 years with the youngest patient being 4 days old and the oldest being 92 years old (Table 1). Previous history of skin disease was positive in 44 patients (51.76%) and 28 of them were suffering from eczema. The most common diseases in order of frequency were eczema 32.94%, drug reaction 23.52%, psoriasis 21/18% and malignancy 8.23% (Table 2). According to our findings, the second most common cause of erythroderma was drugs among which carbamazepin and penicillins were the two most common (Table 3). Malignancies associated with erythroderma are presented in Table 4.

**DISCUSSION**

Erythroderma is defined as diffuse erythematous dermatitis involving all or almost the entire skin. The skin becomes red, dry and scaly. A burning sensation and pruritus are usually present. Erythroderma is a rare but severe and life-threatening disorder with many different underlying causes. Because both the clinical manifestations and histopathologic findings of erythroderma are usually non-specific, it is impossible to detect the precise underlying causes in many cases. The condition usually affects older people and some of its etiologies are lethal, so it is necessary to establish its etiology as soon as possible in order to facilitate its precise and immediate management. Awareness of the most frequent causes of erythroderma can help us to develop an efficient diagnostic strategy and often results in appropriate management of the disease.

To our knowledge, this study is the first report of the incidence and causes of erythroderma from Khuzestan Province in the southwest of Iran. The incidence of erythroderma in our study was about 0.27 per 100,000 people per year, which is much lower than other studies in other parts of the world. The annual incidence of erythroderma in the Netherlands is 0.9 patients per 100,000 and in Finland is 1-2 per 100,000 but Sehgal and Srivastava from India reported an incidence of 35 per 100,000. The mean age of our patients was 49.11 years that is similar to the study of Akhyani et al from Tehran-Iran reporting a mean age of 46.2 years but was higher than the 41.6 years reported from Pakistan and lower than 61 years reported from Finland. The male to female ratio in our study was 1.6, similar to the 1.85 reported by Akhyani et al from Tehran. This ratio was

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Male</th>
<th>Female</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>0-9</td>
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<td>4</td>
<td>3</td>
<td>8.23</td>
</tr>
<tr>
<td>10-19</td>
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<td>4</td>
<td>10.59</td>
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<tr>
<td>20-29</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>3.53</td>
</tr>
<tr>
<td>30-39</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>12.94</td>
</tr>
<tr>
<td>40-49</td>
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<td>5</td>
<td>10.59</td>
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<tr>
<td>50-59</td>
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<td>7</td>
<td>5</td>
<td>17.12</td>
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<td>60-69</td>
<td>16</td>
<td>12</td>
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<td>18.82</td>
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<td>70-79</td>
<td>11</td>
<td>6</td>
<td>5</td>
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</tr>
<tr>
<td>80-89</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>5.88</td>
</tr>
<tr>
<td>90-99</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>2.35</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>52</td>
<td>33</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2. Dermatoses as the causative factor of erythroderma**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczema</td>
<td>28</td>
<td>32.94</td>
</tr>
<tr>
<td>Drugs</td>
<td>20</td>
<td>23.52</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>18</td>
<td>21.17</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
<td>8.23</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td>2</td>
<td>2.35</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>1</td>
<td>1.17</td>
</tr>
<tr>
<td>Pemphogus foliceous</td>
<td>1</td>
<td>1.17</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>1</td>
<td>1.17</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>8.23</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>100%</td>
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</tbody>
</table>
1.85 in Pakistan and 1.94 in Finland but 2.25 in Thailand. Previous history of skin disease was found in 44 patients (51.76%) and 28 (32.9%) of them were suffering from eczema. The most common disease was eczema (32.94%), followed by drug reaction (23.52%); these findings are different from a report from Finland that showed 42% and 10% respectively; in addition, 12% developed erythroderma due to contact reaction to topical drugs. In Thailand, pre-existing dermatoses were seen in 38% and drugs reactions were seen in 23% of the patients. These results in Pakistan were 74.4% and 5.5% respectively, which are much different from our study. Regardless of the causes of erythroderma, the pathology reports are usually suggestive of eczema but the exact diagnosis should not only be based on the pathology report. The large differences between our study and Pakistan’s may be due to the method of diagnosis in their study or other unknown factors. It should be noted that the percentage of eczema in Pakistan’s study is much higher than other reports.

Onset of erythroderma due to drug reactions is typically sudden and rapid, and its resolution is typically faster than cases of erythroderma due to other causes. A notable exception occurs when erythroderma accompanies systemic drug hypersensitivity reactions due to antibiotics, anticonvulsants, and allopurinol. Hypersensitivity develops within 2 to 5 weeks after the medication is started and may persist for weeks despite discontinuation of the medication, but the best prognosis as clearing of erythroderma is in the drug reaction group. Most drugs can cause erythroderma. Drugs as an etiologic group had the second highest percentage in our series; one reason may be very low drug costs in Iran, the fact that physicians prescribe many drugs in one visit. Therefore, because patients are frequently on many different drugs, it is often difficult to determine which drug is responsible. In an erythrodermic patient, any drug should be considered a potential factor. Generally, it is attributed to the drug most recently added. In our findings, the agents of greatest risk for inducing erythroderma were carbamazepine followed by penicillins.

Malignancy is definitively associated with erythroderma (most commonly cutaneous T-cell lymphoma (CTCL)). About 8.23% of our cases were secondary to malignancy and the most common type of malignancy was Mycosis Fungoides (MF). In some studies, a much higher percentage of malignancy has been reported. For example, up to 25 -40% of erythroderma are secondary to MF. Patients with chronic erythroderma without a defined etiology and a high index of suspicion for CTCL or other underlying malignancies must be maintained. Because erythroderma is occasionally associated with internal malignancies, even patients with previous history of known dermatoses whose clinicopathologic features are inconclusive should be investigated carefully to rule out malignant neoplastic causes. In 8.23% of our patients, no causes were found; these patients are classified as idiopathic. The percentage of idiopathic patients varies in most erythrodermic series. The diversity of the incidence of each cause of erythroderma in various studies seems to be related to the variability of investigative procedures and follow-up. In idiopathic cases, if the patients are followed up for a long time, a significant proportion of them will progress to Cutaneous T Cell Lymphoma. So, repeated skin biopsies are recommended as the best method for etiologic diagnosis of erythroderma.

In our study, only 52 out of 85 patients had skin biopsy records. In other patients, the diagnoses were determined based on history, course and clinical presentation of the diseases. Our patients, who had MF, all had skin biopsy records suggestive of MF. A patient with hepatocellular carcinoma had

### Table 3. Drugs associated with erythroderma

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepin</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Penicillins</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Co-Trimoxazole</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 4. Malignancies associated with erythroderma

<table>
<thead>
<tr>
<th>Type of malignancy</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
<td>3</td>
<td>42.85</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>14.28</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1</td>
<td>14.28</td>
</tr>
<tr>
<td>Adenocarcinoma of the prostate</td>
<td>1</td>
<td>14.28</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>14.28</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>100</td>
</tr>
</tbody>
</table>
Erythroderma in Khuzestan province, southwest of Iran

non-specific skin histopathology and a patient with lymphoma had a positive lymph node and skin biopsy. All patients with unknown diagnosis had more than one skin histopathologic records with nonspecific changes. There are significant differences in the frequency of causes of erythroderma in different epidemiological studies, possibly due to differences in criteria and methods of selection of patients in these studies. Almost all studies are retrospective and patient selection is based on either initial condition at the time of admission, or in the middle and during the treatment or final diagnosis at the time of discharge. To overcome these biases and problems, it is better to design prospective studies.

Erythroderma is a rare but serious skin disorder. Awareness of the most frequent causes can help us to develop an efficient strategy for diagnosis and appropriate management of the disease. The results of this study may serve as a guide to identify the causes in new erythrodermic patients, at least in Khuzestan.

REFERENCES

Bilateral congenital nevus of Ota in association with Mongolian spot

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INTRODUCTION

Nevus of Ota, a dermal melanocytic nevus first described in Japan ¹, manifests as blue - black or gray-brown patchy/diffuse pigmentation that usually occurs unilaterally in areas innervated by the first and second branches of the trigeminal nerve ². Bilateral involvement is an exception, especially if it is congenital, as in our case. Hereunder, we report an interesting case of association between bilateral “congenital” nevus of Ota and Mongolian spot.

CASE REPORT

A 24-year-old woman presented with asymptomatic hyperpigmented bilateral patches on her temples, eyelids and forehead since birth. Furthermore, the patient had a congenital grey patch, compatible with Mongolian spot, on her buttock. She had no vascular or other cutaneous lesion. Histopathologic examination revealed bipolar dendritic melanocytes dispersed in a ribbon-like pattern between the collagen fibers and around the neurovascular bundles of the dermis. As far as we know, this is the first case of bilateral “congenital” nevus of Ota in association with a Mongolian spot reported in a patient.

Keywords: nevus of Ota, congenital nevus, dermal melanosis, mongolian spot, bilateral nevus.

A 24-year-old woman presented with asymptomatic hyperpigmented bilateral patches on her temples, eyelids and forehead since birth. Furthermore, the patient had a congenital grey patch, compatible with Mongolian spot, on her buttock. She had no vascular or other cutaneous lesion. Histopathologic examination revealed bipolar dendritic melanocytes dispersed in a ribbon-like pattern between the collagen fibers and around the neurovascular bundles of the dermis. As far as we know, this is the first case of bilateral “congenital” nevus of Ota in association with a Mongolian spot reported in a patient.
DISCUSSION

Nevus of Ota (Nevus fuscoceruleus ophthamo-maxillaris) was first described by a Japanese dermatologist in 1939. Ota nevus can be congenital or acquired in adolescence. It occurs almost entirely in persons of Asian descent. The clinical manifestations are usually unilateral; only 5 percent of cases are bilateral. Clinically, blue-gray macular pigmentation with irregular borders involves skin that is innervated by the first and second branches of the trigeminal nerve. Histopathology of the affected skin shows the presence of dendritic cells containing melanin in the dermis.

Extracutaneous manifestations include ocular involvement of sclera, episclera, conjunctiva, cornea, retina, and the uveal tract. Similar discoloration can be observed in the oral mucosa (buccal and palatal), as well as in nasal mucosa and the tympanic

Figure 1. Hyperpigmented bilateral congenital patches on the face and sclera

Figure 2. Blue-grey hyperpigmentation of the sclera and face (closer view)

Figure 3. Mongolian spot on the left buttock of patient.

Figure 4. Histopathologic view of the facial lesion: dispersed melanocytes in a ribbon-like pattern between collagen fibers in the dermis (H&E *40)
membrane. Leptomeninges can also be affected. Open angle glaucoma and malignant melanoma involving the eyes are rare associations reported 3.

Nevus of Ota has been associated with idiopathic facial neuralgia, Sturge Weber syndrome 4, ipsilateral sensory neural hypoacusia, neurofibromatosis 5, primary retinitis pigmentosa and multiple blue nevi 6. Malignant transformation of the nevus of Ota to melanoma has been reported several times. Melanoma arising in the choroid, brain, orbit, iris, ciliary body, or optic nerve in association with a nevus of Ota has been described; therefore, careful observation is mandatory in these patients 6.

Various therapies have been successfully used. Cosmetic cover-up products can be used for camouflage. Cryosurgery and microsurgical treatments can leave disfiguring scars and are not recommended. Combined dermabrasion and the carbon dioxide snow method have produced good results 7. In recent years, use of laser therapy has been very effective and has given new hopes to patients with the nevus of Ota. The best results for the treatment of this condition are achieved with Q-switched Nd-YAG, ruby, and alexandrite lasers or a combination of them 8. Although there are some reports of bilateral nevus of Ota in literature 9, 10, almost all of them are acquired. The point of this case is that it was congenital. As far as we know, this is the first reported case of bilateral “CONGENITAL” nevus of Ota in association with Mongolian spot in a patient.

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Localized genital bullous pemphigoid; A case report

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CASE REPORT

A 22-year-old married man was visited at Valiasr Hospital Clinic with a one-year history of erosive lesion on the ventral surface of his penis and scrotum (Figure 1). He had been treated by different antibiotics and topical therapy without any success.

Upon dermatologic examination, he was observed to have an erosive macerated lesion on his genitalia (the ventral surface of the penis and scrotum) with no lesion or bulla in other parts of the body. His physical examination was otherwise normal. He had no drug history or trauma. In the result of his laboratory tests, potassium hydroxide smear, gram stain and culture, Tzank smear and VDRL, HCV Ab, HBS Ag and HIV serology were negative. Also, skin biopsy showed subepidermal blister (Figure 2).

Bullous pemphigoid (BP) is an autoimmune bullous disorder with urticarial pruritic papules and plaques and tense bullae in flexural surfaces of body. The localized form of the disease is a rare variant which can be triggered by different stimuli. Hereunder, we report a patient with the local type involving genitalia without any triggering factors.

Keywords: bullous pemphigoid, localized, genitalia

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Figure 1. The erosive lesion on the ventral surface of the penis and scrotum.

Figure 2. Subepidermal blister with cellular infiltration (H&E*10).
and linear deposits of C3 and IgG were reported on direct immunofluorescence techniques (DIF). The diagnosis of bullous pemphigoid was made regarding the clinical and histopathological data. Our patient responded well to treatment with oral prednisolone 50 mg/day for one month followed by gradual tapering of the dose. There was no recurrence of the disease at the time of this report.

DISCUSSION

Some autoimmune bullous disorders such as pemphigus and linear IgA disease may be induced by trauma and PUVA therapy 1,2. Localized BP is a rare variant of BP that may also occur after trauma 3. Some scholars consider it as the result of different forms of epidermal damage (Koebner phenomenon) in predisposed patients; with the induction of antigen exposure in the context of subclinical pemphigoid followed by activation of the corresponding autoimmune process 4, but our patient had no history of trauma. Also, the local form of the disease has been reported following thermal burn, radiation, PUVA therapy, surgical wound and also at injection and colostomy sites 5-10. There are a few reports of localized genital BP in adults; in one of these reports, a 72-year-old woman had pruritic erythematous plaques and erosions in her perineum and perianal area 11. This patient already had chronic itching due to chronic intertrigo or lichen sclerosis before suffering from BP, this factor was postulated as a trigger. In comparison, our patient was younger and had no triggering factor. In another report, a 67-year-old man had pruritic blisters on his penis and scrotum 12, but our patient had no blisters. Similar to our case, a report was found in the literature in which the patient had erosive lesions on her genitalia 13.

Although localized BP in vagina, perineum and perianal area have already been reported, sexual activity can also be considered as one of the triggering factors causing this type of the disorder. The authors believe that sexual activity was most probably the cause in our patient as well. However, it is highly recommended that bullous disorders such as BP be considered in every patient with localized erosive dermatosis with no response to conventional therapy.

REFERENCES

Unilateral generalized morphea: A case report

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INTRODUCTION

Morphea includes a group of diseases that show sclerosis of skin and subcutaneous tissue. Although it generally shows small limited lesions, it may also shows deep lesions causing functional or cosmetical deformites. About 75% of morphea patients are 20-50 years of age and it is 2.6 times more common in women than men. Environmental factors may play a triggering role in the onset of the illness. Thirteen percent of the patients with morphea have generalized morphea. If morphea plaques are seen in at least two of seven anatomical sites (head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, body, face, trunk), the diagnosis is generalized morphea. “Unilateral generalized morphea” form is seen quite rarely.

CASE REPORT

A 14 year-old male patient came to our clinic with spotting lesions starting on the left side of the body. He only complained of the stiffness of the lesions and pruritus, and had no prior history of trauma. On dermatologic examination, hard hyperpigmented indurated lesions with diameters ranging from 0.5 to 10 cm were present on the

Figure 1. Hyperpigmented indurated plaques with diameters ranging from 0.5 to 10 cm on the left thigh and left leg.

Figure 2. Hyperpigmented indurated on the extensor surface of the left arm.
front of the left shoulder, left arm extensor surface, the left surface of the back, left thigh, left leg and left foot (Figure 1, 2). Laboratory tests including antinuclear antibody, complete blood count, sedimentation analysis, rheumatoid factor levels were normal. Initial diagnoses were lichen sclerosus et atrophicus, lupus panniculitis and morphea. Deep punch biopsy specimens were taken from one of the lesions. The histopathological examination of the samples revealed orthokeratosis with an atrophic squamous epithelium. In the dermis, diffuse fibrotic tissue was seen with mononuclear inflammatory infiltrative cells around the blood vessels. Adnexal structures were normal (Figure 3). Considering clinical and histopathological findings, the patient was diagnosed with morphea and received potent topical steroids twice daily and intra-lesional triamcinolone acetonide injection three times per month. At the end of the third month, the lesions improved significantly.

**DISCUSSION**

Morphea is a localized form of scleroderma and is characterized by sclerotic plaques. The fibrotic reaction is limited to the skin and visceral involvement is uncommon ². Morphea has five subtypes as plaque, generalized, bullous, linear and deep ³. About 75% of morphea patients are 20 to 50 year-old women and it is 2.6 times more common in women. Thirteen percent of morphea patients have generalized morphea ¹. Morphea may be triggered by environmental factors including trauma, infections (measles, varicella, Epstein-Barr virus, Borellia Burdorferi), malignancies and radiation therapy ⁴. Our patient had no triggering factors. Morphea pathogenesis is similar to systemic scleroderma as endothelial cells, inflammatory cells and fibroblasts are involved ¹. If morphea plaques are seen in at least two of seven anatomical sites, then the diagnosis of generalized morphea was made ¹. In our patient, morphea plaques were seen on the left arm, left leg, left side of the body. ‘Diffuse morphea’ covers large areas of the body and has an insidious onset.

The chest wall involvement in patients with severe thoracic deformity may cause difficulty in breathing. Despite widespread cutaneous involvement in generalized morphea, internal organs involvement is rare. Arthralgia is seen by 9% of the patients ¹. There was no systemic signs or symptoms in our patient. Circulating auto-antibodies can be detected in morphea like other autoimmune connective tissue diseases ¹. Laboratory findings such as serum ANA, ssDNA antibodies, eosinophilia, antihistone antibodies and hypergammaglobulinemia are more common in linear and generalized morphea ¹. Laboratory tests were normal in our patient. Histopathologic findings of morphea vary according to the stage of the disease and the biopsies taken. Biopsy should be taken to include the subcutaneous tissue. In the biopsies from the peripheral edge of an active lesion, lymphocytes, macrophages, plasma cells and mast cells can be seen; sometimes, intense inflammatory infiltrates with eosinophilia may also be seen ⁵. In our patients, biopsies were taken from the active margin of the lesion. Histopathologic examination was consistent with morphea. In contrast to localized morphea, generalized morphea lesions usually do not tend to regress spontaneously. The effect of strong topical corticosteroids can be increased with intralesional triamcinolone injection. Systemic glucocorticoids, antimalarials, azathioprine and phototherapy are not usually very effective ⁵. Although controversial results exist about inhibitory influence of salazopyrin (Sulfasalazine) on the fibroblast proliferation, some authors have reported good results with salazopyrin (Sulfasalazine) in the treatment of generalized morphea ⁶. Our patient received strong effective topical steroids twice daily and intra-lesional triamcinolone acetonide injection three times per month. At the end of
the third month, a significant improvement was seen in the lesions.

Unilateral generalized morphea is a newly described type of generalized morphea. It has been very rarely reported in the literature. Nagayi et al, reported a 6 year-old boy with unilateral generalized morphea on the right side of his lower leg, trunk, and upper arm. The levels of antinuclear antibodies, rheumatoid factor, and anti single-stranded DNA antibody were elevated. No severe deformities or functional disabilities were noted. With topical corticosteroid therapy, the sclerotic skin became gradually softer, and no progression of sclerosis was noted for one year. Kraigher et al, reported a 20-year-old healthy Jewish woman of Yemenite origin who presented with a 2-year history of a linear eruption on the right shoulder and thorax, upper and lower arm, dorsal surface of the hand, and lower leg. Gerçeker Turk et al, presented a case of unilateral generalized morphea that was triggered by vibration. They proposed that development of ipsilateral generalized morphoea without pulmonary involvement in a left handed marble worker indicated exposure to hand–arm vibration rather than to silica as an aetiologial factor in this condition. Appelhans et al, reported four cases of unilateral generalized morphea. We decided to present this case because of the rarity of the disease and for the purpose of literature review.

REFERENCE

Acquired hyperpigmented lesion on the foot

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CASE

A 3.5-year-old girl presented with a 1-year history of a slow
growing pigmented lesion on the dorsal aspect of her right foot.
Physical examination revealed the presence of a pigmented patch
with color distribution from pink to tan to dark brown, relatively
well circumscribed and approximately 1.5 × 2cm with irregular
borders, and especially a single dark central papule superimposed
in the middle of it (Figure 1). The lesion had a soft consistency and
the child did not have any other symptoms. During the last year, it
had increased in dimensions and thickness.

The remainder of her physical examination was insignificant.
Also, there was no positive family history of a particular disease
or any history of trauma or drug usage. A 3 mm punch biopsy was
obtained from the central dark papule and the specimen was sent
for histopathologic examination.

What is your diagnosis?

Figure 1. A pigmented plaque with color distribution from pink to dark brown on the dorsal aspect of the left foot.

Figure 2. The histopathology view: intradermal nests of large epithelioid cells with a polygonal shape, occasional
multinucleation, and a strongly eosinophilic cytoplasm
(H&E × 10)
ACQUIRED HYPERPIGMENTED LESION ON THE FOOT

DIAGNOSIS

Spitz nevus

Microscopic findings

The histopathology of the specimen revealed a well-circumscribed and symmetrical lesion which was composed of intradermal nests of large epithelioid cells with polygonal shape, occasional multinucleation, and a strongly eosinophilic cytoplasm (Figure 2). The nuclei were large with smooth nuclear membranes and prominent nucleoli (Figure 3). There was no mitosis or necrotic cell. The clinical and histopathological features were consistent with diagnosis of spitz nevus.

DISCUSSION

The Spitz nevus, named after Sophie Spitz who first described it in 1948, is also known as benign juvenile melanoma and spindle and/or epithelioid cell nevus. The lesion was originally believed to occur largely in children, but it is now well recognized in young to early middle-aged adults. The prevalence of Spitz nevus has not been accurately documented in the general population. However, Spitz nevus account for approximately 1% of melanocytic lesions. Spitz nevi are mostly acquired, but congenital ones have been reported as well. They are seen in all age groups but are uncommon beyond the age of 40 to 50 years. The lesions in adults are more pigmented than in children.

No particular etiologic factors have been found. They may be derived from the same progenitor cells that give rise to epidermal melanocytes and nevomelanocytes. Amplifications of chromosome 11p and H-RAS and activating mutations of H-RAS have been noted in a subset of Spitz nevi. Spitz nevi vary in size from 2 mm to 2 cm or more, with an average diameter of approximately 8 mm. Most commonly, they are well circumscribed, dome-shaped papules or nodules varying in color from pink to tan to dark brown. Generally, the color is homogeneous and the margins are well defined. Relatively flat polypoid and pedunculated morphologies have also been described. Occasionally, lesions may have erosions and scale-crust. Telangiectasia is seen frequently. The head and neck area is probably the most common site, accounting for 42% of lesions in one series. Other parts of the body can be affected less frequently. It often has a recent onset, but a small percentage of nevi may be present for many years.

Atypical Spitz nevi refer to lesions demonstrating one or more (usually a constellation of) features that deviate from conventional Spitz nevi. The features may include a large size (e.g. > 1 cm in diameter), asymmetry, deep involvement of the dermis or subcutis, ulceration, easily found dermal mitoses (>2-3 mitoses/mm²), being specially deep, a significant pagetoid spread, prominent confluence and high cellular density of melanocytes in the dermis, and lack of maturation.

Histologically, these lesions display striking nests of large epithelioid cells, spindle cells or both, usually extending from the epidermis into the reticular dermis in an inverted-wedge configuration. The closely apposed nests of cells within a uniformly hyperplastic epidermis often contribute to a so-called ‘raining-down’ appearance. Both mononuclear and multinucleate giant epithelioid cells are frequently observed. These cells extend into the subjacent dermis as both single cells and as nests or fascicles. Occasional bizarre cytologic features, necrotic cells and mitotic figures are found within even the most banal lesions. Differentiation from a melanoma can often be very difficult and occasionally even impossible. Some
features that favor the diagnosis of Spitz nevus are a symmetric shape, sharp lateral demarcation maturation in depth, tadpole and multinucleated giant cells and lack of upward epidermal spread.

The clinical differential diagnosis of Spitz nevi is wide and includes other melanocytic nevi, particularly dermal nevi, hemangiomas, pyogenic granuloma, verrucae, molluscum contagiosum, juvenile and adult xanthogranulomas, dermatofibroma, mastocytoma, clear cell acanthoma, insect bite reactions, seborrheic keratoses, epidermal nevus and adnexal tumor. The most important diagnostic problem is the histologic differentiation of Spitz nevus from cutaneous melanoma. Complete excision with margins free of tumor is recommended for all Spitz nevi. However, there are clinicians who reserve this recommendation for lesions with any atypical feature (clinically or histologically) or Spitz nevi in adults. Patients with atypical lesions should be evaluated every 6 to 12 months.

REFERENCES

A case of contact dermatitis due to green bean

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Editor,

Beans are the basic food for human beings. Allergic reaction to beans is not common. However, it is possible since there are many proteins in the beans. Here, the author would like to introduce a case of contact dermatitis due to green bean. A case of 23 year old female patient presented to the physician complaining of itching sensation at both hands. The symptom occurred after she performed hand squeezing on the green beans in distilled water. The patient gave no previous history of allergy to bean. On examination, both of the patient’s hands showed scaly erythematous plaques. The primary presumptive diagnosis is the contact dermatitis to green bean. This case was prescribed for antihistamine drug and topical steroid (0.1% Triamcinolone acetonide lotion) and the symptoms disappeared within a day. The patient performed self-trial of exposure to distilled water and there was no symptom. However, when she performed additional trial by squeezing green beans in distilled water again, she developed symptom and has to visit to the physician again. She repeatedly performed this self-trial for 3 times. Although this case did not agree for having skin biopsy or other sero-immunodiagnoses, the repeated exposure to the bean by the mean of skin rubbing provocative action for several times lead to the same dermatological presentation. Hence, this case was finally diagnosed to be a case of contact dermatitis due to green bean. Generally, green bean is seldom reported as an allergen. However, green bean as food allergen is uncommon 1. The non-specific lipid transfer protein (Pha v 3) of green bean is identified as the main inducer of allergic reaction 2. In some rare cases, the induction of asthma and rhinitis is reported 3. Nevertheless, the allergic dermatitis is more extremely rare 4. Hence, this case report is a very rare case to be documented.

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Erratum

The author names of article “Malva Sylvestris in the treatment of hand eczema. Vol. 13, No. 54, winter 2010” is corrected as follows:

Barikbin Behrooz, Maarefat Afsaneh, Rahgoshai Rayhaneh, Moravvej Hamideh, Mohtasham Nahid, Yousefi Maryam, Ameri Simindokht
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