Table of Contents

**Original articles**

Comparative effectiveness of purpuragenic 595 nm pulsed dye laser versus sequential emission of 595 nm pulsed dye laser and 1,064 nm Nd:YAG laser: a double-blind randomized controlled study
Manuel António Campos, Ana Cristina Sousa, Paulo Varela, Armando Baptista, Nuno Menezes

Leprosy in the post-elimination era: a clinico-epidemiological study from a northern Indian tertiary care hospital
Tasleem Arif, Syed Suhail Amin, Mohammad Adil, Konchok Dorjay, Dinesh Raj

Combination of CO2 laser therapy and curettage for sebaceous gland hyperplasia
Hossein Kavoussi, Mansour Rezaei, Mahtab Azimi, Reza Kavoussi

Pityriasis rosea: elucidation of environmental factors in modulated autoaggressive etiology and dengue virus infection
Mehak Singh, Manoj Pawar, Antonio Chuh, Vijay Zawar

Pulsed-dye laser versus intraleisional *Candida albicans* antigen injection in treatment of genital warts
Eman Hamed Elmaadawy, Shaimaa Saeed Shams, Doaa Salah Hegab, Raghd Ahmed Zaki

**Review articles**

Galectin 1 in dermatology: current knowledge and perspectives
Efstathia Pasmatzi, Christina Papadionysiou, Alexandra Monastirli, George Badavanis, Dionysios Tsambaos

Trichotillomania: a psychopathological perspective and the psychiatric comorbidity of hair pulling
Sarah Anwar, Mohammad Jafferany

**Short report**

Successful treatment of extensive uremic calciphylaxis with intravenous sodium thiosulfate and its potential in treating various diseases of pathologic calcification
Sandra Burja, Alen Jovic, Robert Ekart, Nejc Piko, Jovan Miljkovic, Vesna Breznik

**Case reports**

Isolated collagenoma on the face: a rare occurrence
Fouzia Siraj, Sharma Shruti, Geeti Khuller, Ashok Saxena

Atrophoderma of Pasini and Pierini in a young adult: a case report
Antigona Begolli Gerqari, Mybera Ferizi, Idriz Gerqari

Unusual photodermatosis with lichenoid eruption and apoptosis in a 33-year-old female
Jordan M. Montoya, David J. DiCaudo, Aaron R. Mangold, David L. Swanson Agata Maciejewska-Radomska, Waldemar Placek
Retraction

Retraction note: Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report

Editorial expression of concern: The measurement of serum TNF-α levels in patients with lichen planus
Comparative effectiveness of purpuragenic 595 nm pulsed dye laser versus sequential emission of 595 nm pulsed dye laser and 1,064 nm Nd:YAG laser: a double-blind randomized controlled study

Manuel António Campos1✉, Ana Cristina Sousa1, Paulo Varela1, Armando Baptista1, Nuno Menezes1

Abstract

Introduction: Erythematotelangiectatic rosacea is a common condition in Caucasians. The most frequently used lasers to treat this condition are pulsed dye laser (PDL) and neodymium:yttrium-aluminum-garnet laser (Nd:YAG). This study compares the treatment efficacy of purpuragenic PDL with that of sequential emission of 595 nm PDL and 1,064 nm Nd:YAG (multiplexed PDL/Nd:YAG).

Methods: We performed a prospective, randomized, and controlled split-face study. Both cheeks were treated, with side randomization to receive treatment with PDL or multiplexed PDL/Nd:YAG. Efficacy was evaluated by spectrophotometric measurement, visual photograph evaluation, the Dermatology Quality of Life Index questionnaire, and a post-treatment questionnaire.

Results: Twenty-seven patients completed the study. Treatment was associated with a statistically significant improvement in quality of life (p < 0.001). PDL and multiplexed PDL/Nd:YAG modalities significantly reduced the erythema index (EI; p < 0.05). When comparing the degree of EI reduction, no differences were observed between the two treatment modalities. PDL was associated with a higher degree of pain and a higher percentage of purpura. Multiplexed PDL/Nd:YAG modality was associated with fewer side effects and greater global satisfaction, and 96.3% of the patients would recommend this treatment to a friend.

Conclusions: Both laser modalities are efficacious in the treatment of erythematotelangiectatic rosacea. The multiplexed PDL/Nd:YAG modality was preferred by the patients.

Keywords: pulsed dye laser, Nd:YAG, effectiveness, rosacea treatment

Received: 8 June 2018 | Returned for modification: 25 September 2018 | Accepted: 3 October 2018

Introduction

Erythematotelangiectatic rosacea is a common condition in Caucasians, affecting up to 10% of the population (1). The most frequent locations are the nose, bilateral cheeks, the chin, and the forehead (2). The most frequently used laser to treat this condition is pulsed dye laser (PDL). One can also use intense pulsed light (IPL), and more recent studies have shown the efficacy of microsecond neodymium:yttrium-aluminum-garnet (Nd:YAG) (3–11). Studies have suggested that a combination of multiple wavelengths in the treatment of vascular lesions could provide additional efficacy and reduction in purpura (12, 13). Multiplexed PDL/Nd:YAG is a laser modality that corresponds to a 595 nm pulsed dye laser fired milliseconds before a 1,064 nm Nd:YAG laser beam, and some authors have suggested that this multiplexed PDL/Nd:YAG modality is efficacious for treating recalcitrant rosacea (14). The advantages of combining both laser modalities have been attributed to the ability of PDL in transforming oxyhemoglobin into methemoglobin before the Nd:YAG laser fires. PDL was reported to enhance Nd:YAG laser absorption in vascular structures by a factor of three to five, which allows the use of lower fluences, thus reducing the risk of side effects (15). This study compares the effectiveness of purpuragenic PDL with that of multiplexed PDL/Nd:YAG (595 nm/1,064 nm).

Study devices

One laser device (Cynergy with Multiplex, Cynosure, Westford, MA, USA) with two different modalities (purpuragenic 595 nm PDL vs. multiplexed PDL/Nd:YAG) was used for the two arms of the study. The PDL settings were fluence of 6.0 J/cm², spot size of 7 mm, pulse duration of 0.5 ms, dynamic cooling device (DCD) level 3 of 5, and one pass with an overlap of 10%. The multiplexed PDL/Nd:YAG settings were PDL fluence of 7.0 J/cm², Nd:YAG laser fluence of 35 J/cm², spot size of 7 mm, pulse duration of 10 ms for PDL and 15 ms for Nd:YAG laser (long-delay), DCD level 3 of 5, and one pass with
minimal overlap in order minimize the risk of thermal injury. These settings were standard company settings for the treatment of erythematotelangiectatic rosacea. When the nose was affected, we used the same randomization as the malar region. Other affected regions were treated with the last laser used. Only one pass was used (if areas were missed during the treatment, we did not retreat those areas).

**Randomization protocol**

The left or right side of each patient’s face was randomized to a treatment modality using a random number generator. Each given assignment was sealed in an opaque, sequentially numbered envelope given to the patient by one investigator (MAC).

**Study procedures**

Each cheek received treatment with either PDL or either multiplexed PDL/Nd:YAG at 3- to 4-week intervals. After each treatment session, a questionnaire (Supplementary material 1) was delivered to the patient and returned at the following visit. Visual analog scales were used to rate pain (1 to 10), degree of purpura (expressed in %), and global satisfaction (expressed in %). The Dermatology Life Quality Index (DLQI) questionnaire (16) was completed in order to evaluate improvement in quality of life (QoL), standard digital photographs were taken, and erythema quantification with a spectrophotometer was obtained at baseline, before each session, and 1 month after the last treatment. Adverse events reported by the patient or observed by the investigator were recorded.

**Topical skin procedures**

The face was gently cleansed with chlorhexidine gluconate 0.2% before treatment. All patients applied broad-spectrum SPF 50 sunscreen immediately after each treatment and were instructed to use sunscreen daily.

**Blinding**

Patients were unaware of which cheek received which laser modality. Both laser treatments were performed in the same room by a different investigator (NM). The investigator taking the spectroscopy measurements (MAC) was blinded regarding allocation and did not assist in the laser treatments.

**Photographs**

After removing all makeup, digital single-lens reflex (SLR) photographs were obtained of the face from the front, and the right and left lateral positions. A third independent investigator (PV) evaluated the photographs taken and rated the improvement in erythema on a four-grade scale as previously described by Karsai et al. (9): Grade 1 was defined as clearance of less than 10% of the redness, Grade 2 as clearance of 10 to 50% of the redness, Grade 3 as clearance of 51 to 90% of the redness, and Grade 4 as clearance of more than 90% of the redness.

**Spectrophotometer**

A Mexameter MX 18 (Courage + Khazaka, Germany) quantified the erythema index (EI) from both sides of the face at three points: Point A = 2 cm below the midpupillary line, Point B = 4 cm below the midpupillary line, and Point C = 6 cm below the midpupillary line (Fig. 1). Three measurements were obtained at each point, and a mean was recorded. In order to compare efficacy between both lasers, the mean EI difference (mean EI after the third treatment minus mean EI at baseline) was calculated for both lasers. All measurements were performed in the same office at a controlled room temperature of 20°C and patients were instructed to avoid hot beverages (e.g., coffee or tea) prior to the observation.
measurements, and patient questionnaire are presented in Table 1.

Overall, we observed a statistically significant reduction in DLQI in our study ($p < 0.001$). The reduction in DLQI occurred after just one treatment, with a reduction of mean DLQI of 6.35 to 3.30 ($p < 0.001$). Further reduction was observed between the reported DLQI after the second treatment (3.30 vs. 1.74; $p = 0.018$) and third treatment (1.74 vs. 1.22; $p = 0.001$).

As assessed by visual photographic evaluation, mean improvement in erythema was maximum after just one treatment (mean clearance of 10 to 50%) in both laser modalities and did not improve with further treatments. EI was significantly reduced at Points B and C with multiplexed PDL/Nd:YAG modality ($p = 0.002$ and $p = 0.007$, respectively) and with PDL modality ($p = 0.004$ and 0.005, respectively). At Point A, both lasers failed to demonstrate a significant reduction in EI ($p = 0.585$ and $p = 0.287$, respectively). When we compared the mean EI difference (EI after third treatment – EI at baseline) between the two lasers, we did not observe a statistical difference in the three measurement points (Point A: $p = 0.231$; Point B: $p = 0.674$; Point C: $p = 0.966$).

PDL was associated with a higher degree of pain (mean value) in all treatment sessions when compared to multiplexed PDL/Nd:YAG modality (5.93 ± 2.9 vs. 5.11 ± 2.6 after the first session; 5.89 ± 2.4 vs. 5.0 ± 2.5 after the second session; 5.33 ± 2.9 vs. 5.04 ± 3.0 after the third session). PDL modality was also associated with a higher reported pain score (mean value) in the first 3 days after treatment (3.61 ± 3.0 vs. 3.41 ± 3.0 after the first session; 2.89 ± 2.7 vs. 1.74 ± 2.0 after the second session; 2.44 ± 3.2 vs. 1.67 ± 2.2 after the third session). Side effects were significantly more common with PDL after every session, and purpura was the most common side effect. The most frequently reported side effect with multiplexed PDL/Nd:YAG was edema. When patients were asked to classify the purpura in the 1st week after each treatment, PDL was associated with a higher percentage of purpura than multiplexed PDL/Nd:YAG (63.70 ± 21.3 vs. 20.74 ± 27.2 after the first session; 51.92 ± 24.2 vs. 26.15 ± 27.1 after the second session; 57.41 ± 27.7 vs. 27.0 ± 25.1 after the third session). The percentage of purpura after PDL as reported by the patient decreased after each session of treatment, despite not achieving statistical significance ($p = 0.063$). Multiplexed PDL/Nd:YAG achieved a superior global satisfaction score (%) than PDL (65.15 ± 27.7 vs. 46.54 ± 26.2 after the first session; 61.85 ± 27.7 vs. 59.26 ± 23.2 after the second treatment; 67.8 ± 22.2 vs. 61.85 ± 20.0 after the third session). In both laser modalities, global satisfaction increased significantly after each session ($p = 0.046$ and $p = 0.001$). At the end of the study, when patients were asked if they would recommend this treatment to a friend with the same condition, 96.3% would recommend multiplexed PDL/Nd:YAG modality and 70.4% would recommend PDL modality.

**Discussion**

We studied the efficacy of two laser modalities, PDL and multiplexed PDL/Nd:YAG, in the treatment of erythematotelangiectatic rosacea in a consecutive series of 27 patients. Because every patient received both modalities, we believe our study represents the most appropriate method to compare these two treatment modalities. The evaluation of efficacy combining the use of visual assessment, spectrophotometer measurements, the DLQI, and the patient questionnaire makes our study the most complete comparison between these two treatment modalities. To our knowledge, no previous study of rosacea has attempted a spectrophotometric comparison between these two laser modalities.

An important point that must be highlighted in our study is that different investigators performed visual assessment (PV), spectrophotometric comparison between these two laser modalities.

### Table 1 | Description of Dermatology Life Quality Index (DLQI), photograph evaluation, spectrophotometer measurements, and patient questionnaire.

<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>Baseline</th>
<th>First treatment</th>
<th>Second treatment</th>
<th>Third treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLQI (mean ± SD)</td>
<td>6.15 ± 4.9</td>
<td>3.30 ± 3.5</td>
<td>1.74 ± 1.6</td>
<td>1.22 ± 1.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Photographic erythema improvement (mean %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDL</td>
<td>10–50</td>
<td>10–50</td>
<td>10–50</td>
<td>10–50</td>
<td>–</td>
</tr>
<tr>
<td>Spectrophotometer erythema index (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG at Point A</td>
<td>526.7 ± 127.9</td>
<td>537.3 ± 111.4</td>
<td>542.1 ± 97.2</td>
<td>537.0 ± 103.9</td>
<td>0.585</td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG at Point B</td>
<td>591.9 ± 96.9</td>
<td>559.0 ± 113.0</td>
<td>559.7 ± 111.2</td>
<td>537.7 ± 93.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG at Point C</td>
<td>520.1 ± 119.7</td>
<td>509.2 ± 95.2</td>
<td>498.1 ± 116.7</td>
<td>465.7 ± 114.6</td>
<td>0.007</td>
</tr>
<tr>
<td>PDL at Point A</td>
<td>534.7 ± 113.2</td>
<td>526.4 ± 106.1</td>
<td>550.6 ± 85.4</td>
<td>525.9 ± 91.5</td>
<td>0.287</td>
</tr>
<tr>
<td>PDL at Point B</td>
<td>585.6 ± 99.4</td>
<td>575.4 ± 85.0</td>
<td>563.2 ± 85.1</td>
<td>537.6 ± 97.8</td>
<td>0.004</td>
</tr>
<tr>
<td>PDL at Point C</td>
<td>520.5 ± 95.5</td>
<td>497.0 ± 91.3</td>
<td>494.3 ± 96.3</td>
<td>465.2 ± 99.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Pain during treatment (0 to 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG</td>
<td>5.11 ± 2.6</td>
<td>5.0 ± 2.5</td>
<td>5.04 ± 3.0</td>
<td>–</td>
<td>0.948</td>
</tr>
<tr>
<td>PDL</td>
<td>5.93 ± 2.9</td>
<td>5.89 ± 2.4</td>
<td>5.33 ± 2.9</td>
<td>–</td>
<td>0.253</td>
</tr>
<tr>
<td>Pain during first 3 days (0 to 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG</td>
<td>1.59 ± 2.0</td>
<td>1.74 ± 2.0</td>
<td>1.67 ± 2.2</td>
<td>–</td>
<td>0.894</td>
</tr>
<tr>
<td>PDL</td>
<td>3.41 ± 3.0</td>
<td>2.89 ± 2.7</td>
<td>2.44 ± 3.2</td>
<td>–</td>
<td>0.202</td>
</tr>
<tr>
<td>Side effects observed (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG</td>
<td>4 (14.8)</td>
<td>7 (25.9)</td>
<td>9 (33.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PDL</td>
<td>15 (55.6)</td>
<td>15 (55.6)</td>
<td>13 (48.1)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Purpura in first week after treatment (0 to 100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG</td>
<td>20.74 ± 27.2</td>
<td>26.15 ± 27.1</td>
<td>27.0 ± 25.1</td>
<td>–</td>
<td>0.122</td>
</tr>
<tr>
<td>PDL</td>
<td>63.70 ± 21.3</td>
<td>51.92 ± 24.2</td>
<td>57.41 ± 27.7</td>
<td>–</td>
<td>0.063</td>
</tr>
<tr>
<td>Global satisfaction with treatment (0 to 100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG</td>
<td>56.15 ± 27.7</td>
<td>61.85 ± 27.7</td>
<td>67.8 ± 22.2</td>
<td>–</td>
<td>0.046</td>
</tr>
<tr>
<td>PDL</td>
<td>46.54 ± 26.2</td>
<td>59.26 ± 23.2</td>
<td>61.85 ± 20.0</td>
<td>–</td>
<td>0.001</td>
</tr>
<tr>
<td>Recommendation of this treatment to a friend (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplexed PDL/Nd:YAG</td>
<td>22 (81.5)</td>
<td>23 (85.2)</td>
<td>26 (96.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PDL</td>
<td>17 (63.0)</td>
<td>19 (70.4)</td>
<td>20 (70.4)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Both treatment modalities have similar efficacy. Similar to previous studies (1, 2), our study population had a predominance of females (63.0%), and 88.9% of the patients were older than 30.

Our baseline DLQI index (6.15) is in line with previous studies, demonstrating that our study population is comparable in terms of the DLQI (16). As demonstrated in previous studies (17–20), our patients had a significant improvement in QoL, reflected by the statistical reduction in the DLQI. Interestingly, the improvement in QoL was achieved after the first treatment, but it continued to improve significantly after the second and third sessions of treatment. Because our patients received both treatment modalities, we cannot specify whether the improvement in QoL was attributed more to PDL or multiplexed PDL/Nd:YAG. Despite this limitation, we can conclude that both treatment modalities significantly improved QoL. Further studies are needed to evaluate QoL improvement with multiplexed PDL/Nd:YAG modality.

Visual photograph evaluation did not differ in the two laser modalities. Maximum improvement (10 to 50% clearance) was obtained after one session and did not improve with further treatments. Because different scales have been used to evaluate improvement of erythema, the comparison between studies is troublesome. Despite these difficulties, a previous study reported a higher degree of clearance (mean clearance of 10 to 50% with PDL and mean clearance of 51 to 90% with multiplexed PDL/Nd:YAG), although this study only evaluated telangiectasias of the nose (9).

Both laser modalities significantly reduced EI at two of the three points evaluated. The lack of statistical significance at Point A may be attributed to a lesser degree of involvement in this area and consequently to a reduced improvement in erythema in this location. EI reduction had already been demonstrated in PDL and IPL (10), but not with multiplexed PDL/Nd:YAG or with long-pulsed Nd:YAG laser. We did not observe differences when comparing the degree of EI reduction between the two laser modalities, suggesting that both treatment modalities have similar efficacy.

Our study reported more side effects with PDL than with multiplexed PDL/Nd:YAG modality. As previously reported, purpura induced by PDL is a major outcome problem for patients (3, 9, 10, 17, 19, 21–23). As expected, PDL was associated with a higher degree of purpura than multiplexed PDL/Nd:YAG, although this side effect decreased after the second and third sessions. PDL was also associated with more pain during the treatment and in the following 3 days when compared to multiplexed PDL/Nd:YAG. Edema was the most common side effect with multiplexed PDL/Nd:YAG modality. Multiplexed PDL/Nd:YAG modality achieved higher global satisfaction by patients in each session, and more patients would recommend this treatment modality to a friend with the same condition. Interestingly, global satisfaction significantly increased for both laser modalities after each session. To our knowledge, this improvement in global satisfaction had not been described previously.

We are aware that our study has a limited number of participants. Nevertheless, we included a consecutive series of patients, and the number of participants in our cohort is actually higher when compared to most previous studies (3, 9, 17, 21–23). Between-subject variations were minimized by our study design, in which split-face comparison was used within the same subjects. Taking into account that these laser modalities have proved efficacy in treating erythematotelangiectatic rosacea, we did not include split-face subjects with a no-treatment control. Although split-face comparisons within the same patient reduces variability, we acknowledge that our study design may have not overcome all variances due to the small sample size. Spectrophotometric measures have been described as liable and they depend on room temperature and cutaneous vascular tone (21, 23). In order to reduce this variability, all measurements were performed at controlled room temperature.

We conclude that both laser modalities are efficacious in the treatment of erythematotelangiectatic rosacea. Despite demonstrating similar efficacy, multiplexed PDL/Nd:YAG modality was associated with fewer side effects and a higher satisfaction rate by patients. Taking these results into account, we believe the choice between both modalities must be individualized and discussed with patients.

References
SKRAŠAN POUZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

TREMFYA®

Prvi selektivni inhibitor IL-23.

TREMFYA®

PRVI SELEKTIVNI INHIBITOR IL-23.

NAD PSORIAZO S PLAKI

Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih.

Ime zdravila: Tremfya 100 mg raztopina za injiciranje v napolnjeni injekcijski brizgi

Kakovostna in količinska sestava: Ena napolnjena injekcijska brizga vsebuje 100 mg guselkumaba v 1 ml raztopine. Pomožne snovi: histidin, histidinijev klorid monohidrat, polisorbat 80, saharoza, voda za injekcije.

Indikacije: Zdravljenje zmerne do hude psoriaze s plaki pri odraslih, ki so primerni za sistemsko zdravljenje.

Odmerevanje in način uporabe: Priporočeni odmerek je 100 mg s subkutano injekcijo v tednih 0 in 4. Sledi vzdrževalno odmerjanje vsakih 8 tednov. Izogibati se je treba injiciranju na mestih, ki kažejo znake psoriaze. Pri bolnikih, pri katerih je do 16 tednov zdravljenja ni odziva, je treba razmisliti o prenehanju zdravljenja. Prilagajanje odmerka pri starejših (starih 65 let ali več) ni potrebno. Priporočil za odmerjanje pri bolnikih z okvaro ledvic ali jeter ni mogoče dati, ker zdravila pri teh skupinah dnevnih učinkov. Varnosti in učinkovitosti zdravila pri otrocih in mladostnikih, mlaših od 18 let, niso ugotoviti.

Kontraindikacije: Resna preobčutljivost na učinkovino ali katero koli pomožno snov; klinično pomembna, aktivna okužba (npr. aktivna tuberkuloza).

Posebna opozorila in previdnostni ukrepi: Zdravilo lahko poveča tveganje za razvoj okužb. Bolnikom s klinično pomembno aktivno okužbo se zdravljenja ne sme uvesti, dokler okužba ne izzveni oziroma ni ustrezno zdravljena. Pred začetkom zdravljenja z guselkumabom je treba bolnikom pregledati in opraviti preiskave na prisotnost tuberkuloze. Bolnike, ki prejema guselkumabom je treba med in po začetku zdravljenja spremljati glede znakov in simptomov aktivne tuberkuloze. Pri bolnikih z latentno ali aktivno tuberkulozo se zdravljenja ne sme uvesti, dokler okužba ne izzveni oziroma ni ustrezno zdravljena.

Nosečnost, dojenje in plodnost: Ženske v rodni dobi morajo med zdravljenjem in še najmanj 12 tednov po njem uporabljati učinkovite kontracepcijske metode. O uporabi guselkumaba pri nosečih ali bedenih cesarstvih se je pripraviti pred začetkom zdravljenja. Ženske, ki prejema guselkumabom, s svojimi partnerji morajo razporediti pravilna kontracepcijske metode.

Neželeni učinki: okužbe zgornjih dihal, gastroenteritis, okužbe z virusom Herpes simplex, dermatofitije, glavobol, diareja, urtikarija, artralgija, eritem in bolnečina na mestu injiciranja (vsi NU so opisani v povzetku glavnih značilnosti zdravila).

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze s plaki.

Prva linija sistemskega zdravljenja psoriaze s plaki.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdravljenja psoriaze.

Prva linija sistemskega zdraval
Leprosy in the post-elimination era: a clinico-epidemiological study from a northern Indian tertiary care hospital

Tasleem Arif1, Syed Suhail Amin1, Mohammad Adil1, Konchok Dorjay1, Dinesh Raj1

Abstract

Introduction: Leprosy is a chronic disease caused by Mycobacterium leprae. Despite being eliminated from India in 2005, there are still a considerable number of leprosy cases.

Methods: A prospective hospital-based study involving all leprosy patients attending the leprosy clinic at the Department of Dermatology from January 2015 to December 2016.

Results: A total of 220 patients visited the leprosy clinic during the study period. Most of the patients (48.7%) were 20 to 40 years old. Multibacillary disease was more common in females (84.7%) than males (67.6%), and in rural patients (80.9%) than urban patients (64.8%). Borderline lepromatous leprosy was the most common (38.2%) type of leprosy seen, followed by lepromatous leprosy (28.2%) and borderline tuberculoid leprosy (21.4%).

Conclusions: Despite elimination, leprosy continues to be a health problem in this part of the world. We have shown that females and the rural population are more susceptible to multibacillary disease.

Keywords: borderline lepromatous, borderline tuberculoid, leprosy, multibacillary disease, Mycobacterium leprae

Received: 12 April 2018 | Returned for modification: 22 November 2018 | Accepted: 12 December 2018

Introduction

Leprosy, or Hansen's disease, is a chronic disease that primarily involves the skin and peripheral nerves. It has a variety of clinical presentations, depending on the cell-mediated immunity of the host. It has been classified by the World Health Organization (WHO) as a paucibacillary disease and multibacillary disease depending on the number of lesions. The Ridley–Jopling classification of leprosy divides the disease into five groups: tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and lepromatous (LL). The Indian classification includes an additional pure neuritic variant. The diagnosis of leprosy is clinical, but a slit skin smear and histopathology are means to aid diagnosis (1).

Despite being known to mankind since time immemorial and the discovery of the causative agent more than a century ago, many aspects of the epidemiology and pathogenesis of leprosy still remain to be fully elucidated. Sustained efforts helped India achieve elimination targets of leprosy in 2005 (i.e., a prevalence of less than one case per 10,000 at the national level). Despite this, leprosy remains a health concern in India. More than 60% of all new leprosy patients detected in the world were Indians (2). The prevalence of leprosy currently stands at 0.68 cases per 10,000 population per 2012–2013 data (3). Although this share seems small, it corresponds to a huge number of leprosy cases on the ground due to India’s large population. This inspired the authors to carry out a prospective study at our leprosy clinic to determine its clinical-epidemiological trends in our population.

Methods

We conducted a prospective study on all new leprosy patients attending the leprosy clinic at the dermatology department at our hospital. The duration of our study was 2 years, from January 2015 to December 2016. The data collected included the patients’ age, sex, residence, and type of leprosy. Informed consent (verbal and written) was provided by the patients or their guardians for slit skin smear examination and skin biopsy for participation in the study, and for subsequent publication of the data, which may also contain their personal details, including their images. Consent for nerve biopsy was obtained in selective cases. The patients were enrolled in the study only after meeting the above requirements for consent. The patients were diagnosed on the basis of clinical signs and symptoms, and the diagnosis was confirmed by slit skin smear and skin histopathology in all cases. Regarding leprosy reactions, only those cases of reactions were added to the database in which the initial presentation at the time of enrollment in the study was a reaction. However, reactions developing later during follow-up were not added to the database.

Clinical diagnosis

Any patient with one of the following symptoms was provisionally diagnosed with leprosy, and the diagnosis was further augmented with histopathological examination of a skin biopsy: a) hypopigmented or erythematous skin lesion(s) with either definite loss or impairment of sensation, b) peripheral nerve involvement as demonstrated by definite thickening with sensory impairment, and c) slit skin smear examination positive for acid-fast bacilli.

Classification of disease

The disease was classified according to Jopling’s classification into five categories: TT, BT, BB, BL, and LL (1). Patients presenting only with nerve thickenings and impairment of sensations without skin lesions were diagnosed as having pure neuritic leprosy, and their diagnosis was confirmed by nerve biopsy employing the sural nerve. Histoid leprosy was diagnosed when patients presented...
with papular and nodular lesions, confirmed by histopathology through the predominance of spindle-shaped cells and unusually large numbers of acid-fast bacilli.

**Multibacillary and paucibacillary disease**

Multibacillary disease was considered when patients had more than five skin lesions or more than one nerve involvement or skin smear positive at any site. Paucibacillary disease was diagnosed if there were five or fewer skin lesions or no nerve involvement, or if there was only one nerve involved and the skin smear was negative at all sites. At any point in time, skin smear positivity was considered multibacillary disease irrespective of the number of skin lesions or number of nerves involved (3).

**Treatment of leprosy**

WHO multidrug therapy was used in the management of leprosy. Paucibacillary disease was treated with rifampicin 600 mg once a month (supervised) and dapsone 100 mg daily (self-administered) for a duration of 6 months, which has to be completed within 9 months. Multibacillary disease was treated with rifampicin 600 mg once a month (supervised), dapsone 100 mg daily (self-administered) and clofazimine 300 mg once a month (supervised), and 50 mg daily (self-administered) for a total duration of 12 months, which has to be completed within 18 months. The patients received their drugs in monthly calendar blister packs. For children under 10 years, the drug doses were rifampicin 450 mg (300 mg + 150 mg) once a month, dapsone 50 mg daily, and clofazimine 150 (three 50 mg capsules) once a month and 50 mg daily. For children younger than 10 years, the dose was adjusted according to body weight.

The statistical method used in the study for comparison between groups was the chi-square test. A p-value less than 0.05 was considered statistically significant.

**Results**

A total of 220 new leprosy patients attended the leprosy clinic during the study period. Of these, 148 were males and 72 were females (p = 0.03). The various characteristics of the patients are presented in Tables 1, 2, and 3.

**Table 1** Distribution of patients by age.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>11–20</td>
<td>42</td>
<td>19.1</td>
</tr>
<tr>
<td>21–30</td>
<td>49</td>
<td>22.3</td>
</tr>
<tr>
<td>31–40</td>
<td>58</td>
<td>26.4</td>
</tr>
<tr>
<td>41–50</td>
<td>41</td>
<td>18.6</td>
</tr>
<tr>
<td>51–60</td>
<td>23</td>
<td>10.4</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>5</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>220</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table 2** Distribution of patients by sex and type of leprosy.

<table>
<thead>
<tr>
<th>Leprosy type</th>
<th>Rural</th>
<th>Urban</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>TT</td>
<td>10</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>BT</td>
<td>38</td>
<td>17.3</td>
<td>41</td>
</tr>
<tr>
<td>BB</td>
<td>6</td>
<td>2.7</td>
<td>9</td>
</tr>
<tr>
<td>BL</td>
<td>48</td>
<td>21.8</td>
<td>64</td>
</tr>
<tr>
<td>LL</td>
<td>40</td>
<td>18.2</td>
<td>68</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>2.7</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>148</td>
<td>67.3</td>
<td>72</td>
</tr>
</tbody>
</table>

**Table 3** Distribution of patients by residence and type of leprosy.

<table>
<thead>
<tr>
<th>Leprosy type</th>
<th>Rural</th>
<th>Urban</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>TT</td>
<td>6</td>
<td>2.7</td>
<td>6</td>
</tr>
<tr>
<td>BT</td>
<td>16</td>
<td>7.3</td>
<td>31</td>
</tr>
<tr>
<td>BB</td>
<td>6</td>
<td>2.7</td>
<td>3</td>
</tr>
<tr>
<td>BL</td>
<td>52</td>
<td>23.6</td>
<td>32</td>
</tr>
<tr>
<td>LL</td>
<td>33</td>
<td>15.0</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0.9</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>52.3</td>
<td>105</td>
</tr>
</tbody>
</table>

**Discussion**

The mean age of our patients was 35, with the youngest 8 years old and oldest two patients 80 years old. More than 80% of patients were between 11 and 50 years old. The greatest numbers of patients were 31 to 40 years old. The incidence of leprosy is said to rise between ages 10 and 20 and to peak between ages 20 and 35 (4). Other studies also corroborate this finding (5, 6). Leprosy in children (16 years or younger) was of the same proportion as observed in other studies (5, 7, 8). The share of children with multibacillary disease was 69.2%. Similar results were shown by Mukherjee et al., who found 61.3% of children with multibacillary disease (9). However, other studies have shown that paucibacillary disease is more common in children (10). This disparity may be due to a delay in seeking medical care due to poor socioeconomic status and lack of awareness. The male:female ratio in our study was 2:1. This is in accordance with other recent studies from India showing almost the same results for predilection by sex (5, 9).

Multibacillary disease was confirmed in 161 (73.2%) patients, of whom nine (4.1%) patients were in the BB segment, 84 (38.2%) patients in the BL segment, and 62 (28.2%) patients had LL disease. One hundred males (67.6%) and 61 females (84.7%) had multibacillary disease, implying that multibacillary disease is more prevalent than the paucibacillary type, and it was statistically significant (p = 0.003). Multibacillary disease was seen in 91 (80.9%) rural patients and 68 (64.8%) urban patients, and this approached statistical significance (p = 0.05).

Paucibacillary disease was seen in 59 (26.8%) patients. Of the 59 patients with paucibacillary disease, 12 (5.4%) had TT and 47 (21.4%) had BT disease. There were also two patients with histoid leprosy and four patients with pure neuritic leprosy. Out of 148 males, 48 (32.4%) had paucibacillary disease, whereas only 11 (15.3%) females had this disease. Twenty-two rural patients (19.1%) had paucibacillary disease and 37 urban patients (35.2%) had the same.

Three patients (1.4%) presented to us with type 1 reaction and 21 patients (9.5%) presented with type 2 reaction at the first visit. Twenty-two patients (10%) had grade 1 deformity and four patients (1.8%) presented with a trophic ulcer. Six patients (2.7%) defaulted on their treatment and did not complete it.
from all over western Uttar Pradesh, an indicator of the lack of availability of good medical care facilities in rural areas.

In our study, 73.2% patients had multibacillary disease. This corresponds to the percentage of multibacillary cases in our state as well as other studies (9, 14, 15). However, some studies have reported a slightly lower percentage of multibacillary cases (8, 16). The proportion of leprosy cases with multibacillary disease is reflective of patients that are a major source of infection and are also susceptible to reactions and consequently deformities (16, 17). The greater proportion of multibacillary leprosy cases also indicates the inability of health services to diagnose early cases of leprosy. Moreover, patients tend to hide their lesions due to the associated stigma. The greater number of multibacillary cases in our study is probably due to these reasons because our hospital caters to the most underprivileged section of society in the economically backward Indian state of Uttar Pradesh. A total of 63.6% patients were in the borderline category (including BT, BL, and BB disease), whereas 28.2% had LL and only 5.4% presented to us with TT. Borderline cases have become more common since the introduction of multidrug therapy as opposed to the polar forms of the disease that were more commonly seen in the dapsone era (11, 18–20). The low percentage of polar TT in our study is similar to observations by Jindal et al., who reported 5.52% cases of TT (21). We found that a higher percentage of female patients than male patients had multibacillary disease. This is in contrast to the observations of other studies, which report the multibacillary form of leprosy to be more common in males (9). Arora et al. found the number of males and females with LL to be almost equal, but the BL and BB cases were more common in females (15). The increased number of females with multibacillary disease in our study might be explained by the poor socioeconomic status of females, leading to delay in seeking medical care. Most of the women in our study were also married and engaged in the household activities, which can serve as a barrier for reporting their disease. In low socioeconomic conditions, the husband works long hours for the family and it is difficult for him to leave work and accompany his wife to the hospital. Apart from this, the stigma of leprosy has a more marked effect on females than males, which can further delay a woman’s appointment for her skin lesions if she suspects leprosy. Urban patients in our study had a lower percentage multibacillary disease compared to patients from rural areas. Mohite et al. also found that multibacillary disease was more commonly diagnosed if the patient came from a rural area (13). This is possibly due to the rural population’s lack of access to medical facilities.

Lepra reactions were seen in 10.9% of patients, with type 2 reaction being much more common than type 1 reaction. Similar observations were made by Salodkar et al., who observed reactions in 11.1% of cases, with type 2 reaction being four times more frequent than type 1 reaction (22). This implies that many patients ignore their disease and seek medical care only when they develop reactions. Other studies have shown an even higher percentage of patients presenting with lepra reactions (15, 16, 23). It is worth noting that we documented patients for reactions only at the patient’s first visit. These data do not include patients that developed reactions after treatment was initiated. The number of defaulter in our study was 2.7%. Good counseling of patients is necessary to maintain patient adherence to treatment. Type 1 lepra reaction is associated with a sudden alteration of cell-mediated immunity associated with a shift in the patient’s position in the leprosy spectrum. Type 1 reaction is a type IV hypersensitivity reaction usually observed in the borderline spectrum of the disease. There is an increase in inflammation of some or all preexisting skin patches or plaques, which become erythematous, swollen, and tender. Type 2 lepra reaction (T2R) is usually associated with immune complexes and is observed in LL. It is an example of type III hypersensitivity reaction and is usually associated with systemic symptoms. Clinically, there is a sudden appearance of crops of new evanescent, pink to rose-colored papules, nodules, or plaques varying in size that are painful and tender to the touch (24). In our study, type 2 reaction scored more than type 1 probably because our study population had a good number of LL cases. In addition, these cases were first-time presentations of the disease as a reaction and not follow-up cases that subsequently developed reactions.

Various control and preventive programs are already underway in India. These include the national leprosy control program, national leprosy eradication program, modified leprosy elimination campaign, and national rural health mission. Integration of leprosy services with the general care system to cover the entire population, trained leprosy workers at the peripheral level, regular surveillance of new cases at the community level, improving the quality of services, improving community awareness and involvement, and home visits to diagnosed patients are preventive and control measures that are being carried out. An accredited social health activist (ASHA) is one of the key components of the national rural health mission. The ASHA is a female health activist that belongs to village, and so she can be used to reach female leprosy patients specifically (25).

Because our study was conducted at a tertiary care hospital, it certainly is not representative of the situation in the field. Nonetheless, it offers a general picture of current leprosy trends in the region. The large percentage of patients with multibacillary cases, particularly females and mostly from the rural population, indicates that leprosy awareness and control programs aimed at elimination need to be more vigorously implemented to targeting these segments.

Conclusions

Leprosy may have been eliminated from this part of the world, but it definitely continues to be a health concern. The total number of cases is large, although the percentage is low. This warrants effective and vigorous implementation of awareness about the disease, facilities for investigation, and unhindered provision of therapy. The occurrence of the disease in children is a cause of concern and signifies active disease transmission. Newer strategies to target susceptible groups need to be devised to achieve complete eradication of this menace from society.

References


Combination of CO2 laser therapy and curettage for sebaceous gland hyperplasia

Hossein Kavoussi1 ✉, Mansour Rezaei1, Mahtab Azimi1, Reza Kavoussi1

Abstract

Introduction: Sebaceous hyperplasia (SH) is a common cutaneous disorder associated with cosmetic problems. Some optional treatments and various laser devices have been reported to be effective, but recurrence and cosmetic outcome have not been resolved.

Methods: This interventional study was performed on SH lesions. First, the lesions were treated with a CO2 laser, and then the shrunken lesions were removed with a fine, sharp curette.

Results: A total of 46 patients (32 females and 14 males, mean age 39.9 ± 5.7 years) with SH skin lesions varying in severity were included in this study. The mean time of repair was 11.5 ± 1.9 days; a shorter repair time was seen in females and for mild extension lesions (p < 0.001). A fair cosmetic outcome was seen in 76.1% of cases, with better results reported for females and for skin types II and III (p < 0.001).

Conclusions: The method reported herein is an easy, rapid, and effective procedure for the complete removal of SH lesions with few complications in the majority of patients with numerous lesions and Fitzpatrick skin types II–IV. Cosmetic outcomes are better in females and skin types II and III.

Keywords: CO2 laser therapy, sebaceous gland hyperplasia

Introduction

Sebaceous hyperplasia (SH) is one of the most prevalent causes of benign skin lesions that most often develop in middle age and show an increasing prevalence over time. SH is usually characterized by yellow or skin-colored papules and nodules that are commonly located on the face. The goal in treating it is merely cosmetic improvement (1).

Many treatment modalities with varying cosmetic and treatment results have been suggested for the removal of SH lesions, including systemic isotretinoin (2), topical trichloroacetic acid (3), cryotherapy (4), intralesional electrodessication (5), shave excision and curettage (6), photodynamic therapy (7), and laser therapy (8–16).

CO2 laser therapy is the gold standard and a popular modality for the ablation of most skin lesions, such as those caused by SH, in outpatient clinic procedure rooms. Proper use of a CO2 laser leads to the precision ablation of skin lesions with minimal complications such as hypertrophic or atrophic scarring and post-inflammatory hyperpigmentation (15, 16).

This study was carried out to assess the treatment and cosmetic outcomes of a combination of CO2 laser and curettage treatment for SH lesions.

Methods

Study design and population

This clinical interventional follow-up study was performed on 46 patients at the Hajdaie Dermatology Clinic of Kermanshah University of Medical Sciences in Iran over a period of 18 months in 2016 to 2017.

All participants were informed of the study aims and gave consent to participate before being included. Patients with typical clinical presentations were enrolled in the study; those with atypical manifestations had a histopathologic evaluation done before being included.

Patients with large lesions (larger than 10 mm), pregnant and breastfeeding women, those that had consumed oral isotretinoin in the previous 6 months, and patients with repair abnormalities were excluded from the study.

Demographic data, SH severity, and outcomes of treatment such as recovery time, cosmetic outcome, and complications were recorded on the questionnaire used in this study.

Severity of lesions and cosmetic classification

SH lesions were classified according to severity as limited (<10 lesions), moderate (10–50 lesions), frequent (51–100 lesions), and very frequent (>100 lesions). The cosmetic outcomes were categorized as 1) fair, with minimal or no scarring and no hypo- or hyperpigmentation; 2) moderate, with moderate scarring and/or hypo- or hyperpigmentation; and 3) poor, with prominent scarring and/or hypo- or hyperpigmentation.

Procedural methods (Figs. 1–3)

Topical EMLA was used as anesthesia and, 1 hour after its application, CO2 laser therapy was begun. Patients that could not tolerate the procedure because of pain were injected intralesionally with lidocaine 2%.

Based on their thickness, SH lesions were subjected to 2 to 4 passes of pulsed CO2 laser at 5 to 8 watts and 400 milliseconds pulse duration. Between laser passes, the debris tissue was wiped away with saline-soaked gauze.

Laser therapy resulted in a reduction in thickness, and the extent and altered texture of the lesion tissue from para-lesion normal skin tissue were determined. In this stage, laser-treated lesions...
were removed easily, precisely, and completely using a fine, sharp, disposable curette.

For secondary intention, the induced defect was washed with normal saline and dressed, and repair cream was applied for 7 to 10 days.

The duration of repair time was measured when 1) a significant decrease in ulcer depth was seen, 2) an absence of granulation tissue was noted, 3) a lack of exudation or discharge was observed, 4) there was an absence of ulcer or erosion in the defect, and 5) casting off of the probable eschar was seen.

Patients were evaluated weekly in the 1st month, once every 2 weeks in the 2nd and 3rd months, and then once every 3 months for a total of 12 months. Cosmetic outcomes were assessed after the 4th week or later.

Ethical considerations

This study was approved by the Ethics Committee of Kermanshah University of Medical Science and registered in the IRCT database (IRCT201702016403N7). Participant information was kept confidential.

Statistical analysis

Data were analyzed using the statistical software package SPSS, version 16. Qualitative analysis of the data was done using the chi-square test and Fisher’s exact test. The Kolmogorov–Smirnov test was used to check the normality of the quantitative data. Levene’s test and an independent sample t-test were also used to measure equality of variance and compare the means for the quantitative data of two categories.

Results

This study recruited 46 patients: 32 (69.6%) females and 14 (30.4%) males. The age range of participants was 29 to 54 years with a mean age of 39.9 ± 5.7 years. Skin types II, III, and IV were seen in nine (19.6%), 32 (69.6%), and five (10.9%) patients, respectively. Limited, moderate, frequent, and very frequent lesions were seen in five (10.9%), 12 (26.1%), 24 (52.2%), and five (10.9%) patients, respectively. Cosmetic outcomes were fair, moderate, and poor in 35 (76.1%), nine (19.6%), and two (4.3%) cases, respectively (Table 1).

Cosmetic outcomes in females were fair, moderate, and poor in 30 (93.8%), two (6.6%), and zero (0%) patients, respectively, and in males they were fair, moderate, and poor in five (37.7%), seven (50.0%), and two (14.3%) patients, respectively (p < 0.001). Fair cosmetic outcomes were more common in skin type II (88.9%) and skin type III (84.4%), but poor cosmetic outcomes were more common in skin type IV (40.0%) (p < 0.001). Fair cosmetic outcomes in patients with mild, moderate, frequent, and very frequent lesions were seen in 80.0%, 83.3%, 75.0%, and 60.0% of cases, respectively (p = 0.767). Cosmetic outcomes were significantly better in females (p < 0.001) and in skin types II and III (Table 2).
The mean repair time was 11.5 ± 1.9 days (range 8–15 days; Table 1). The mean repair time was 10 ± 1.6 days in females and 13.1 ± 1.5 in males (p < 0.001). The mean repair times in skin types II, III, and IV were 11.1 ± 2.4, 11.5 ± 1.8, and 12 ± 1.6 days, respectively (p = 0.709). The mean repair times in limited, moderate, frequent, and very frequent lesions were 9.2 ± 1.3, 11 ± 1.85, 11.7 ± 1.6, and 13.8 ± 1.1 days, respectively (p < 0.001). Repair times were significantly shorter in females (p < 0.001) and for limited lesions (Table 2).

During the follow-up, in the 1st month 14 patients had moderate or prominent hypertpigmentation (3rd month: 10 patients, 6th month: nine, 9th month: eight, and 12th month: seven). In addition, in the 1st month six patients had moderate or prominent scarring (3rd month: six patients, 6th month: five, 9th month: five, and 12th month: five).

No recurrence was seen in patients during the follow-up period, but occasionally patients would refer with a few residual lesions, especially those with frequent or very frequent severity or incomplete removal of some lesions. In such situations, the residual lesions were treated in the follow-up period.

Discussion

This study showed that the combination of CO2 laser therapy and curettage is an efficacious, safe, and simple method for the removal of SH lesions with positive cosmetic outcomes in the majority of patients. Cosmetic outcomes were significantly better in females and skin types II and III. Repair time was significantly shorter in females and in those with limited lesions.

Ataş et al. (4) found that cryotherapy was an effective method for treating SH, especially in males. The method used in this study was effective in removing SH lesions in both sexes, but favorable cosmetic results and shorter repair times were seen in females. This may be related to the intrinsic estrogen hormone, which influences wound repair, whereas androgens negatively affect cutaneous wound healing (17). Females are also more sensitive to their cosmetic appearance than males and tend to care more about wound defects.

This study found that skin types II and III experienced better cosmetic outcomes. Sriprachya-Anunt et al. (18) showed that post-inflamatory hyperpigmentation after CO2 laser resurfacing was seen more often in skin type IV. It is concluded that appropriate care of a wound defect, especially avoidance of sunlight, is associated with satisfactory cosmetic outcomes even in dark skin.

In this study, patients with limited lesions had better cosmetic outcomes than patients with very frequent lesions. Extensive SH is more prevalent in men and in more damaged skin (19). This explains why skin repair and cosmetic outcomes are undesirable in abundant lesions.

Although photodynamic therapy is an effective treatment of choice with minimal complications for the removal of SH lesions, it requires multiple sessions and special equipment and is not available at most therapeutic centers (3, 7). The advantages of the method for curing SH discussed herein are the few treatment sessions required and the accessibility of a CO2 laser device at most outpatient clinics.

Aghassi et al. (8) showed that the pulsed dye laser was an effective device for the treatment of SH, but only 28% of lesions completely disappeared with one session. Further limitations of this laser include expensiveness and unavailability (20).

Winstanley et al. (9) and No et al. (11) safely and successfully treated SH lesions using 1,720 nm and 1,450 nm diode lasers, respectively. The small number of cases, the time-consuming nature of the procedure, and most patients’ lack of access to these devices were the main limitations reported for these lasers.

One case report described a man with multiple SH lesions that underwent CO2 laser therapy followed by treatment with low-dose oral isotretinoin for 2 years. He was free of SH lesions over the 3-year follow-up period (21). Long-term systemic therapies, especially highly complicated drugs such as oral isotretinoin, are associated with high costs, more complications, and a lack of patient cooperation.

Kim et al. (13) introduced a simple procedure in a 55-year-old man with multiple SH lesions using the pinhole method with a CO2 laser and acne extractor. This method appears to be somewhat similar to the method discussed in this article, but it requires skilled hands and reports lack a sufficient sample size. Moreover, two CO2 irradiation sessions (one at the beginning and one at the end of this procedure) may increase scar formation.

In the method discussed in this article, SH lesions were first irradiated with a CO2 laser, which induced shrinkage, altered texture consistency, and determined the extent of the lesions. To complete the lesion removal and prevent further thermal damage, a fine, sharp curette was used to easily dislodge the shrunkened sebaceous lobules.

Conclusions

The procedure reported herein is an easy, rapid, and effective treatment of choice with few complications for the complete removal of SH lesions in both sexes, frequent lesions, and Fitzpatrick skin types II–IV. Cosmetic outcomes were better in females and skin type II. It is suggested that further studies evaluate this method and its cosmetic outcomes by assessing cases at several centers and by considering more variables such as the location and size of the SH lesions.

![Image](image_url)
References

Pityriasis rosea: elucidation of environmental factors in modulated autoaggressive etiology and dengue virus infection

Mehak Singh¹, Manoj Pawar²✉, Antonio Chuh³, Vijay Zawar²

Abstract

Introduction: A retrospective epidemiological study was conducted to study seasonal variation in the incidence of pityriasis rosea (PR) and its temporal association with various meteorological variables, and dengue virus infection.

Methods: The study was conducted at a tertiary referral center in Guwahati, Assam, India. We searched for and retrieved all medical records of patients diagnosed with PR by dermatologists from December 1st, 2014 to July 31st, 2017. The diagnosis was made only if the patient fulfilled at least three out of the following four clinical features: 1) herald patch, 2) peripheral collaret scales, 3) predominant truncal and proximal limb distribution of the lesions, and 4) orientation of lesions along the lines of cleavage. For each visit by every patient, we retrieved data for the monthly mean air temperature, mean total rainfall, and mean relative humidity. PR patients that had dengue fever with NS1 antigen and/or IgM/IgG antibody positivity were studied along with healthy controls.

Results: Overall, PR occurred more frequently in the colder months and months with less rainfall. However, these associations were insignificant (p = 0.23, R = -0.38, and R = -0.55, respectively). Upon further examination of the data, we found that the monthly incidence of PR was significantly lower in March and April than the other months during the study period (F = 8.31, p = 0.002). A statistically significant higher incidence was detected in September, November, and December (p < 0.01 for 2014 and 2017, but not in the 2016 seasonal cohort) and also in January and February (p < 0.05 for 2016 and 2017). Interestingly, a retrospective history of dengue fever emerged as a significant correlate.

Conclusions: In our setting, there was significant temporal clustering and seasonal variation among patients with PR. The incidence of dengue fever is significantly correlated with PR.

Keywords: dengue, pityriasis rosea, seasonal variation

Introduction

Pityriasis rosea (PR) is suspected to be associated with an infection. However, an exact cause has not been found. Drago et al. reported human herpesvirus 7 to be the causative agent (1). Other investigators reported findings supporting and refuting such an association. However, the distinct clinical course, a lack of recurrences in most of the patients, and the presence of temporal case clustering support an infectious etiology. Furthermore, seasonal variation, association with respiratory tract infections, and a history of contact with PR patients in some patients do support an infectious etiology (2).

Cluster analysis is a useful approach for elucidating possible infectious etiologies. Several studies have evaluated the presence of clustering in PR (3–12). In 1982, Messenger et al. reported significant spatial-temporal clustering only in female patients with PR and a temporal cluster of 16 patients within a 28-day period (3). However, there was no control and the impact of seasonal variation was not studied. Later on, some studies reported seasonal variation and/or case clustering for patients with PR (4, 8–11), whereas others did not find any significant association with seasonal variation and incidence of PR (6, 12). To the best of our knowledge, no study has reported an association of dengue fever with PR. We thus report here a retrospective study investigating the epidemiology of PR and the incidence of dengue fever and its association with PR at a tertiary referral center in Assam.

Methods

The study was conducted at a tertiary referral center in Guwahati, Assam, India. We searched for and retrieved all medical records of patients diagnosed with PR by dermatologists from December 1st, 2014 to July 31st, 2017. The diagnosis was made only if the patient had fulfilled at least three out of the following four clinical features: 1) herald patch, 2) peripheral collaret scales, 3) predominant truncal and proximal limb distribution of the lesions, and 4) orientation of lesions along the lines of cleavage. These diagnostic criteria were laid down and validated by us (13, 14). For each visit by every patient, we retrieved data for the monthly mean air temperature, mean total rainfall, and mean relative humidity. PR patients that had dengue fever were studied along with healthy controls. The detection of NS1 antigen was done using the Panbio Dengue Early enzyme-linked immunosorbent assay (ELISA) (Inverness Medical Innovations, Australia). The detection of IgM antibodies was done using the Dengue-IgM capture ELISA kit (National Institute of Virology, Pune). IgG anti-dengue antibodies were detected using the dengue IgG capture ELISA (PanBio Pty Ltd, Queensland, Australia).

The following steps were used for the statistical analysis: a) 2 × 2 contingency tables were drawn to calculate the odds ratio (OR) and risk ratio (RR), as well as a chi-square test, and finally a two-tailed Fisher’s exact test (p < 0.05 was considered statistically significant);

1Department of Dermatology and Venerology, H. B. T. Medical College and Dr. R. N. Cooper Municipal General Hospital, Mumbai, Maharashtra, India.
2Department of Dermatology, Dr. Vasanthrao Pawar Medical College, Nashik, India.
3Department of Family Medicine and Primary Care, University of Hong Kong and Queen Mary Hospital, Pokfulam, Hong Kong. ✉Corresponding author: manojpawar624@yahoo.com
b) linear regression model.

Temporal clustering was investigated using a regression model. The monthly incidence of PR was taken as a dependent variable, with meteorological variables such as monthly average temperature, monthly average precipitation, and the occurrence of dengue fever considered as independent variables. The statistical relationship was evaluated using Pearson’s correlation analysis in the statistical software package SPSS (version 20.0, SPSS Inc., Chicago, IL) and online statistics programs.

Time-series analysis

Monthly PR and dengue incidences were cross-correlated using the cross-correlation function (CCF). In a cross-correlation in which the direction of influence between two time series is hypothesized, the influential time series is called the “input” time series and the affected time series is called the “output” time series. The application of cross-correlations in this text refers that the input time series refers to the incidence of dengue in a patient and the output time series refers to an occurrence of an auto-immune response to the dengue virus manifesting as a PR rash.

Results

A total of 136 PR patients were found to fulfill the diagnostic criteria. The male:female ratio was 1.1:1.3. They were between 13 months and 59 years old with maximum incidences in the age clusters 20–29 and 30–39 (Tables 1 and 2).

For the epidemiological data analysis, the seasonality plot indicates a trend characterized by a peak in post-monsoon and winter months (September–January, peak month November) and a trough in summers (peak, April), and the magnitude of the seasonal variation increases at the same rate as the yearly mean levels. Therefore, we tested this distribution pattern to determine whether it was statistically significant. The expected incidence for 12 months was calculated for a year from the total number of new PR patients and the number of hospital working days in each month during the same year. Then the mean ± standard deviation of 3 years was obtained for each month for the expected number of PR patients. Statistical tests were performed to compare actual and expected numbers of first visits during each month. Statistical significance was detected in September, November, and December (p < 0.01 for 2014 and 2017, but not in the 2016 seasonal cohort) and also in January and February (p < 0.05 for 2016 and 2017).

Regarding precipitation and temperature as independent predictive parameters for the incidence of PR, it was found that heavy rainfall is associated with decreased incidence of PR (this correlates with our hypothesis of dengue virus being one of the etiological factors in the development of PR because high rainfall is associated with decreased breeding of the dengue vector (i.e., Aedes mosquitoes) and, as discussed above, increased PR was observed with a drop in temperature.

Temperature and pityriasis rosea (PR) incidence

The regression equation for \( Y \) (where \( Y = \) PR incidence and \( X = \) temperature in Celsius) was \( \hat{Y} = -0.61521X + 58.50307 \) (Fig. 1a). Our interpretation is that the negative value showed an inverse relationship; that is, the incidence of PR increased with decreased temperatures.

Rainfall and PR incidence

The regression equation for \( Y \) (where \( Y = \) PR incidence and \( X = \) rainfall in mm) was \( \hat{Y} = -0.38X + 3.0778 \). The correlation coefficient (PMMC) \( r \) was found to be 0.8714 (\( p = 0.0002 \); highly significant), which shows a positive correla-

Table 1 | Epidemiological data and its comparison with other studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>PR patients</th>
<th>Male:female</th>
<th>Seasonal variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harman et al. (1998)</td>
<td>Eastern Anatolia, Turkey</td>
<td>399</td>
<td>1:1.21</td>
<td>Peak during spring, autumn, and winter</td>
</tr>
<tr>
<td>Nanda et al. (1999)</td>
<td>Kuwait</td>
<td>117</td>
<td>1:1.38</td>
<td>Not reported</td>
</tr>
<tr>
<td>Tay et al. (1999)</td>
<td>Singapore</td>
<td>368</td>
<td>1:19:1</td>
<td>No variation</td>
</tr>
<tr>
<td>Traore et al. (2001)</td>
<td>Burkina Faso</td>
<td>36</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Chuh et al. (2003)</td>
<td>Hong Kong</td>
<td>41</td>
<td>1:1.05</td>
<td>February, July, April</td>
</tr>
<tr>
<td>Chuh et al. (2005)</td>
<td>Minnesota, United States, Kuwait, and Diyarbakir, Turkey</td>
<td>1,379</td>
<td>Not reported</td>
<td>Clusters found but did not mention the seasons</td>
</tr>
<tr>
<td>Sharma et al. (2010)</td>
<td>Uttar Pradesh, India</td>
<td>200</td>
<td>2:1</td>
<td>September to December</td>
</tr>
<tr>
<td>Ayanlowo et al. (2010)</td>
<td>Lagos, Nigeria</td>
<td>427</td>
<td>1:1.55</td>
<td>October, August, March</td>
</tr>
<tr>
<td>Ganguly et al. (2013)</td>
<td>Southern India</td>
<td>73</td>
<td>Male preponderance</td>
<td></td>
</tr>
<tr>
<td>This study (2018)</td>
<td>Northeast India</td>
<td>136</td>
<td>Female preponderance</td>
<td>September to January</td>
</tr>
</tbody>
</table>

PR = pityriasis rosea.
tion between the incidence of Ns1Ag or antibody positivity and PR (Fig. 1c).

I. Cross correlation Function-SARIMA model results – PR:

a) Autocorrelation (ACF) and partial autocorrelation function (PACF) for PR incidence (Figs. 2a–2c):

ACF and PACF plots were deployed to identify patterns in the above data, which are stationary on both mean and variance, to identify the presence of AR (autoregressive) and MA (moving average) components in the residuals. The ACF function shows a perfect sinusoidal pattern with a spike at lag 1; on extrapolating the data to the PAC function, the same correlation is seen at lag 1 ($p = 0.037$).

Figure 1 (clockwise) | 1a: Temperature and pityriasis rosea (PR) incidence, 1b: rainfall and PR incidence, 1c: PR and dengue incidence.

Figure 2a, b, c, d (clockwise) | Original, partial autocorrelation function, and autocorrelation function plots for pityriasis rosea (PR) incidence derived from original time series after prewhitening and SARIMA extrapolation forecast for PR incidence.
b) SARIMA forecast for PR incidence:

For prewhitening, the model SARIMA \((p = 1, d = 0, q = 0, P = 2, D = 1, Q = 2)\) was selected. Strong negative correlation coefficients were found at lags of the 7th and 8th months. Weak negative associations were found at lags of 7 to 9 months (Fig. 2d).

II. Cross correlation Function-SARIMA model results – PR with preceding history of NsAg or antibody positivity (Figs. 3a–3c): Both the ACF and PACF functions showed a significant positive correlation at 0 and 1 lag \((p = 0.028)\).

c) SARIMA forecast for PR cases with Ns1Ag positivity or antibody incidence (Fig. 3d):

A significant positive correlation was found at lag 12 months \((p = 0.04)\). Of the 136 PR patients, 38 were seropositive for either/both IgG and IgM or Ns1Ag \((27.94\%)\) in contrast to 19 \((13.97\%)\) Ns1Ag or IgM and IgG antibody seropositive cases in 136 matched controls. Seropositivity for Ns1Ag or antibody in PR patients was significantly higher than those found in controls \((OR = 2.3878, 95\% CI = 1.294 to 4.4061; RR = 2.95\% CI = 1.217 to 3.2868; Yates \chi^2 = 7.19, p = 0.0073)\), indicating a higher risk of developing PR with a preceding history of dengue viral infection. Furthermore, the bivariate Granger causality for PR incidence and NsAg1 and/or antibody positivity revealed that the incidence of seropositivity to dengue virus infection can be used to forecast the development of PR rash as a significantly positive correlation at lag 2 months \((F = 10.3, p = 0.0237)\).

**Discussion**

This retrospective study found temporal clusters of PR in the dry winter months of September to January, with the correlation being statistically significant for the months of September, November, and December \((p < 0.01\) for 2014 and 2017 but not in the 2016 seasonal cohort) and also in January and February \((p < 0.05\) for 2016 and 2017); however, the overall correlation was weak. The association between the infectious etiology, especially human herpesvirus 6 and 7, with PR is controversial; reasonable evidence suggests that PR is not associated with cytomegalovirus, Epstein–Barr virus, parvovirus B9, picornavirus, influenza and parainfluenza viruses, *Legionella* spp., *Mycoplasma* spp., and *Chlamydia* spp. (15, 16). Interestingly, in this study, the retrospective histories of dengue fever emerged as a significant correlate against a matched cohort of 163 patients visiting the dermatology outpatient department for other ailments. The average duration between the onset of PR and dengue was 78.34 days. The most interesting example of PR with dengue was that of a pair of twins, both of whom presented with typical PR lesions with a history of dengue fever 5 weeks earlier. The outbreaks of dengue occurred from August to October, indicating increased vector transmission in the monsoon and post-monsoon periods. However, we admit that the monthly rate of den-
gue fever may only be a confounding variable. The significance of this should be investigated further in future studies.

The age and sex distribution in our study is in line with other epidemiological studies on PR (3–7). Some of these studies reported a higher incidence of PR during winter (10, 11), whereas one reported a higher incidence in the early rainy season (8) and some reported no seasonal variation (6, 12) (Table 1).

Our study has certain limitations. The most important limitation of this study is that the data were collected at one clinic in one geographical location only. Having adequate resources, we previously performed epidemiological studies in multiple geographical locations (9). However, we lack a similar scale of material support in this study. Confounding variables could thus negate the generalization of our results to other geographical locations and other clinical settings. We also failed to elucidate the underlying mechanisms for our results being similar to or different from those of other investigators (3–11) to an acceptable level of evidence. Although our study followed the morphological features delineated by Drago et al., there is another proposed classification of PR by Chuh et al., in which PR variants, including atypical forms, are classified on the basis of differences in pathogenesis, clinical features, and the course of the disease (19). This classification included pregnant patients, who were not part of our study population.

The temporal clustering documented in this study might suggest a role of dengue virus as an autoimmune trigger, modulated by environmental factors that cause the syndrome in previously unexposed, genetically susceptible individuals, with asymptomatic infection leading to protective immunity in the majority of the population. The fact that PR is self-limited strongly suggests a definitive immune response that terminates the inflammatory process.

Conclusions

We found temporal clusters of PR in the dry winter months of September to January, with the correlation being statistically significant for the amount of rainfall. Interestingly, retrospective histories of dengue fever emerged as a significant correlate. Thus, temporal clustering and dengue infection as significant correlates may imply the infectious etiology of PR. However, the significance of this warrants further multicentric investigations, preferably at different geographic locations.

References

Supplementary data and figures

Statistical methods used

For the cross-correlation function, the correlation coefficient, or Pearson product-moment correlation coefficient (PMCC), was calculated using the formula:

\[ r = \frac{n \sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} y_i}{\sqrt{n \sum_{i=1}^{n} x_i^2 - (\sum_{i=1}^{n} x_i)^2} \sqrt{n \sum_{i=1}^{n} y_i^2 - (\sum_{i=1}^{n} y_i)^2}} \]

where \( n \) is the total number of samples, \( x_i (x_1, x_2, \ldots, x_n) \) are the \( x \) values, \( y_i \) is the \( y \) values, and \( r \) (PMCC) is a numerical value between -1 and 1 that expresses the strength of the linear relationship between two variables. When \( r \) is closer to 1 it indicates a stronger positive relationship.

The cross-correlation calculation for univariate time series was calculated as follows:

The cross-correlation of time series requires the time series to be stationary and prewhitened. Stationarity is defined by a constant mean and equal variance at all times, and it can be achieved by detrending or differencing. Prewhitening removes spurious correlations based on temporal dependencies between adjacent values of the input time series and it removes these influences from the output time series. The parameters lambda, \( d \), and \( D \), and seasonality were used to apply a Box-Cox transformation and (non-)seasonal differencing in order to induce stationarity of the time series. The confidence interval was computed assuming a white noise time series (CI type = white noise).

SARIMA modeling

Multiplicative seasonal auto-regressive integrated moving average (SARIMA) models with all possible combinations of parameters \( p, q, P, Q \in \{0, 1, 2\} \) and with \( d, D \in \{0, 1\} \) were evaluated using Akaike’s information criterion (AIC) on untransformed and logarithmically transformed monthly meteorological data from 2014 to 2017. The selected SARIMA model was then used to prewhiten meteorological data series, PR, and Ns1Ag positivity and PR incidence time series.

For the formulas used, the seasonal ARIMA model incorporates both non-seasonal and seasonal factors in a multiplicative model. One shorthand notation for the model is ARIMA\((p, d, q) \times (P, D, QS)\), with \( p = \) non-seasonal AR order, \( d = \) non-seasonal differencing, \( q = \) non-seasonal MA order, \( P = \) seasonal AR order, \( D = \) seasonal differencing, \( Q = \) seasonal MA order, and \( S = \) time span of repeating seasonal pattern.

The model could be written more formally as:

1. \( \Phi(\Theta^B) = 1 - \Phi(B) - \cdots - \Phi(B^M) \)
2. \( \Theta(B) = 1 + \Theta(B) + \cdots + \Theta(B^N) \)

The seasonal components are:

Seasonal AR: \( \Phi(B^S) = 1 - \Phi(B^S) - \cdots - \Phi(B^S) \)

Seasonal MA: \( \Theta(B^S) = 1 + \Theta(B^S) + \cdots + \Theta(B^S) \)

Analysis was carried out using Wessa online: Wessa P., (2017), (Partial) Autocorrelation Function (v1.0.15) in Free Statistics Software (v1.2.1), Office for Research Development and Education, URL http://www.wessa.net/rwasp_autocorrelation.wasp.
Pulsed-dye laser versus intralesional Candida albicans antigen injection in treatment of genital warts

Eman Hamed Elmaadawy1, Shaimaa Saeed Shams1, Doaa Salah Hegab1✉, Raghda Ahmed Zaki2

Abstract

Introduction: Genital warts are a troublesome therapeutic issue. Pulsed-dye laser (PDL) is a non-ablative therapeutic tool for viral warts. Intralesional Candida albicans (C. albicans) immunotherapy has yielded promising results in treatment of various types of warts. We aimed to evaluate the effectiveness of PDL versus C. albicans immunotherapy for treatment of genital warts.

Methods: Forty adult patients with genital warts were divided into two equal groups; the first was treated using PDL and the second using intralesional C. albicans antigen injection. Treatments were performed at 3-week intervals until complete lesion resolution or for a maximum of three sessions.

Results: PDL yielded higher complete clearance rates (95%) than C. albicans antigen (50%; p = 0.001), which in turn had the advantage of treating distant and internal genital warts. Apart from pain during the session in PDL, both modalities were well tolerated with no recurrence in cured patients during the 16-week follow-up period.

Conclusions: PDL and C. albicans antigen injection are safe and effective treatment alternatives for genital warts. PDL yielded better frequencies of clearance, but C. albicans antigen has additional advantages, including a single injection site and treating distant and internal mucosal uninjected warts, which are usually difficult to treat.

Keywords: genital warts, immunotherapy, laser

Received: 25 September 2018 | Returned for modification: 12 December 2018 | Accepted: 25 December 2018

Introduction

Genital human papilloma virus (HPV) infections are widely prevalent worldwide. Genital warts are associated with a negative impact on the wellbeing of infected men and women as reflected by poorer quality-of-life scores. Moreover, anogenital HPV is the leading cause of cervical cancer, especially with oncogenic high-risk HPV types 16 and 18, in addition to other benign and malignant genital neoplastic lesions (1, 2). HPV types 6 and 11 are low-risk subtypes that are responsible for 90% of the cases of genital warts and rarely give rise to cervical cancers, but they have been associated with some types of verrucous carcinomas such as oral florid papillomatosis and Buschke–Löwenstein tumor (2, 3).

Many different therapeutic options for genital warts currently exist, including imiquimod, podophyllin, interferons (IFNs), cryotherapy, intralesional bleomycin, laser vaporization, electrocautery, and surgical removal. Unfortunately, none of these modalities offer a guarantee of cure, in addition to the common risk of recurrence (4, 5).

Flash-lamp pumped pulsed-dye laser (PDL) emits a wavelength from 585 to 595 nm, consistent with the hemoglobin absorption peak, and it is therefore used for the treatment of vascular lesions. It has shown promising results in the treatment of viral warts because it destroys the characteristically dilated superficial dermal capillaries that supply the warts, thereby starving the epidermal cells harboring viral particles, resulting in wart regression. Furthermore, HPV is heat-sensitive, and that makes it vulnerable to the thermal destructive effect of PDL. PDL is thought to be a safe and effective modality for treatment of warts that can be applied to most body areas (6–8).

Immunotherapy has been tried for warts with oral immune modulators such as cimetidine and levamisole. Several intraligional immunotherapeutic antigens have also been tried, such as Candida albicans (C. albicans) antigen, tuberculain antigens (including purified protein derivative, Mycobacterium w vaccine, and Bacillus Calmette–Guerin), and Trichophyton in addition to measles, mumps, and rubella (MMR) (9). The first antigen that was tried for immunotherapy of warts was that of C. albicans, and the investigators reported success in the majority of patients treated with this test antigen (9, 10).

Intralesional immunotherapy stimulates the host immune system to trigger a delayed-type hypersensitivity response to a multitude of antigens, including the wart tissue. This therapy is associated with the production of a Th1 cytokine milieu and activation of cytoxic and natural killer (NK) cells to fight HPV infection, not only in the local warts, but also affecting distant warts, unlike traditional wart therapies (11). It should be noted that these distant warts, especially if hidden (intravaginal, cervical, intraurethral, or intraanal), are a major therapeutic challenge in HPV affecting the genital area.

Moreover, some cases of genital warts might be associated with dysplasia or carry the risk of future transformation into intraepithelial carcinomas (12), and it should be noted that Buschke–Löwenstein tumors, with invasive growth, recurrence, and possible malignant transformation, are always preceded by condyloma acuminatum (13).

We evaluated the efficacy and safety of PDL versus intralesional C. albicans antigen injection for treatment of genital warts.

Materials and methods

Forty adult patients complaining of genital warts (32 females, 80%; eight males, 20%), whose mean age was 31.92 ± 11.31 (standard deviation [SD]) completed the study. A thorough local genital
examination was performed, including the skin of the lower abdomen, perineum, perianal area, and upper thighs. In males, the penis, scrotum, and urethral meatus were examined. In married females, a cervico-vaginal examination using a Cusco speculum was performed to exclude internal genital warts. Patients with perianal warts underwent proctoscopy for detection of intraanal lesions. All patients included provided signed written informed consent, and the study protocol was approved by the institutional review board of the ethics committee at Tanta University’s Faculty of Medicine.

Patients were divided into two equal groups; the first group was treated with PDL (Deka Synchro VasoQ, Italy) using the following parameters: pulse duration 450 microseconds, spot size 7 to 10 mm (regarding the size of the lesions), and fluence ranging from 7 to 10 J/cm². Up to seven to 10 overlapping pulses were applied to each wart, covering the lesion and 1 mm of surrounding unaffected skin. When necessary, the treatment areas were locally infiltrated with 2% lidocaine hydrochloride before the PDL session. Group II patients were treated using intralesional C. albicans antigen injection (specific hyposensitizing vaccine, C. albicans Allergica; concentration 1:10). The oldest and usually the largest wart (the “mother wart”) was injected intralesionally with 0.3 ml C. albicans antigen solution. In both groups, treatment sessions were performed at 3-week intervals until complete lesion resolution or for a maximum of three sessions. Patients with active local infection, immunosuppression, pregnant females, lactating mothers, and children under 12 were excluded from the study. Patients with a history of photosensitive diseases, active vitiligo, active psoriasis, and keloidal tendency and those on isotretinoin treatment were excluded from PDL group, and those with a history of hypersensitivity to C. albicans antigen and those on beta blockers (because they may become unresponsive to epinephrine in the event of anaphylaxis) were excluded from the C. albicans antigen group.

**Evaluation of efficacy**

Patients were examined and digitally photographed at baseline, at each session of treatment with a notation for the number and size of warts, and after 16 weeks from the last session to assess any recurrence.

The degree of improvement was graded as excellent improvement = total resolution of all warts, marked improvement = 76 to 100% decrease in the number and/or apparent wart size, moderate = 51 to 75%, mild = 26 to 50%, and no improvement = ≤ 25% decline in the number or size of the warts treated. Patients that did not achieve complete clearance after three sessions were offered other treatment options in the form of cryotherapy or trichloroacetic acid.

**Table 1** | Clinical characteristics, treatment outcome, and adverse effects of patients with genital warts treated by pulsed-dye laser (group I) or intralesional Candida albicans antigen immunotherapy (group II).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 20)</th>
<th>Group II (n = 20)</th>
<th>Statistical test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>31.9 ± 11.6</td>
<td>31.95 ± 11</td>
<td>Student’s t</td>
<td>0.014</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (95%)</td>
<td>13 (65%)</td>
<td>Fisher’s exact</td>
<td>5.6</td>
</tr>
<tr>
<td>Male</td>
<td>1 (5%)</td>
<td>7 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>10 (50%)</td>
<td>6 (30%)</td>
<td>Fisher’s exact</td>
<td>2.07</td>
</tr>
<tr>
<td>6–10</td>
<td>3 (15%)</td>
<td>6 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>7 (35%)</td>
<td>8 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of current lesions, months, mean ± SD</td>
<td>4.3 ± 3.9</td>
<td>5.9 ± 6.3</td>
<td>Student’s t</td>
<td>0.97</td>
</tr>
<tr>
<td>Distribution of current lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External genital</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td>Fisher’s exact</td>
<td>1</td>
</tr>
<tr>
<td>Perianal</td>
<td>4 (20%)</td>
<td>4 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraanal</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal genital</td>
<td>0</td>
<td>3 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>0</td>
<td>2 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>0</td>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other partner affected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (31%)</td>
<td>6 (40%)</td>
<td>Fisher’s exact</td>
<td>1.201</td>
</tr>
<tr>
<td>No</td>
<td>11 (69%)</td>
<td>14 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (90%)</td>
<td>18 (90%)</td>
<td>Fisher’s exact</td>
<td>2</td>
</tr>
<tr>
<td>Ablative CO2 laser</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocautery</td>
<td>0</td>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sessions needed for best results, mean ± SD (median)</td>
<td>2.1 ± 0.9 (2)</td>
<td>2.7 ± 0.7 (3)</td>
<td>Fisher’s exact</td>
<td>12.5</td>
</tr>
<tr>
<td>Response to treatment after three sessions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent improvement</td>
<td>19 (95%)</td>
<td>10 (50%)</td>
<td>Fisher’s exact</td>
<td>13.3</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild improvement</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/poor improvement</td>
<td>0 (0%)</td>
<td>5 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects (present/absent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>15 (75%) / 5 (5%)</td>
<td>9 (45%) / 11 (55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>–</td>
<td>17 (85%) / 3 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspigmentation</td>
<td>1 (5%) / 19 (95%)</td>
<td>1 (5%) / 19 (95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>–</td>
<td>17 (85%) / 3 (15%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation, MC = Monte Carlo correction method, p-value = level of significance, * = significant at p < 0.05.
Statistical analysis

Qualitative data were described using numbers and percentages. Quantitative data were described using median and range (minimum and maximum) or mean and SD. Comparison of continuous variables was made using Student’s t-test if normally distributed and the Mann–Whitney test if abnormally distributed, and categorical variables were compared using a chi-square test and, if more than 20% of the cells had an expected count less than 5, correction for chi-square was conducted using Fisher’s exact test or Monte Carlo correction using IBM statistical software package SPSS, version 21. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the baseline clinical characteristics and treatment outcomes of the patients included. The median number of sessions needed for the best results was two sessions for group I and three sessions for group II (p = 0.001). There was statistically significant variation between both groups regarding the degree of clinical response after the third session. In group I an excellent response with complete resolution of the lesions was achieved in five patients (25%) after a single session, in nine patients (45%) after two sessions, and in five patients (25%) after three sessions (Fig. 1). On the other hand, after the three injection sessions in group II, 10 patients (50%) were completely cured with excellent improvement, one patient (5%) showed moderate improvement, two patients (10%) showed mild improvement, and seven patients (35%) showed poor or no improvement. All patients in group II with internal genital warts, either vaginal or cervical, showed clearance of their internal warts due to injection of the external genital mother wart with C. albicans antigen (Fig. 2).

Regarding recurrence, all cured patients in both groups showed no recurrence within the 16-week follow-up period after the last treatment session. Regarding the side effects of PDL therapy in group I, five patients (25%) experienced marked burning pain that required infiltration anesthesia during sessions, and only three patients (15%) developed post-procedural hyperpigmentation. In group II, one patient (5%) developed hypopigmentation at the injection site; three patients (15%) showed flu-like symptoms within 24 hours after the injection, which were relieved by non-steroidal...
anti-inflammatory drugs; 17 patients (87%) developed temporary edema at the injection site, which was relieved by cold compresses; and nine patients (45%) experienced transient mild pain during the day of injection, relieved by analgesics.

In this study, the adverse effects of PDL treatment were minimal. Compared with other destructive modalities used to treat genital warts, there is better patient acceptance, less intense and shorter duration of pain, and minimal disruption in daily activities following PDL treatment. Moreover, no recurrence of genital warts was observed during the 16-week follow-up after the PDL treatment sessions. This lower risk of recurrence of genital warts after PDL treatment has been previously detected by other investigators (22, 23). On the other hand, the results of Komoricki et al. (18) showed no recurrence in the treatment areas, but 22% of their patients developed new genital warts in other locations than those treated after PDL treatment. Badawi et al. (19) reported a recurrence rate of 5% in genital warts after one to three sessions of PDL treatment.

This low incidence of recurrence of warts after PDL sessions could be attributed to its mechanism of action based on laser interaction with wart vasculature and thermal injury to HPV. It has also been postulated that the resulting tissue damage is followed by a cell-mediated immune (CMI) response with up-regulation of lesional interleukin (IL) 2 and IL-4 (24–26). IL-2 plays fundamental roles in immunity through its direct effects on T cells. In addition, on antigenic stimulation IL-2 promotes T cell differentiation into effector and memory T cells, thus helping the body combat infections (27).

Regarding immunotherapy, it is a promising modality for recurrent and/or resistant warts that could lead to clearance of lesions without any local tissue injury or scarring (28).

It should be noted that intralesional C. albicans antigen has shown encouraging results for treatment of common warts in several previous reports (9, 29, 30), but unfortunately it has not been well investigated in genital warts. King et al. (31) studied mumps, Candida, and Trichophyton skin test antigens (0.1 ml each) as single therapies or in combination for treatment of 21 patients with genital warts. The number of sessions was high, reaching 10 sessions in some patients, and a complete response was only seen in those injected with Candida antigen in combination with other antigens (mumps or Trichophyton) (31).

In this study, only 50% of patients with genital warts showed...
complete clearance of their lesions after the third session of \textit{C. albicans} antigen immunotherapy. The results of this study and several others revealed partial or no response in some subjects to \textit{Candida} antigen immunotherapy, and the underlying cause is unclear. Many factors may explain the difference in response between the patients studied, including the degree of sensitivity to the antigen injected, the number, type, size, duration, and resistance of warts, the age and sex of the patients, the level and function of toll-like receptors, the difference in the degree of human leukocyte antigen (HLA) presentation of processed antigen, the difference in the distribution and function of antigen-presenting cells, and the difference in the immune cell response to the processed antigen (26, 30, 32).

In this study, edema after intralesional immunotherapy was the most common side effect (recorded in 85% of patients) and it improved with cold fomentation. King et al. recorded local erythema and edema in 14.28% of their patients; these were transient, lasting less than 24 hours (31).

Hypopigmentation was observed in one patient (5%) in this study at the injection site, which agreed with Wilmer et al. (2013), who reported the occurrence of vitiligo at the injection site of \textit{Candida} antigen for verruca vulgaris in an 8-year-old girl (33). The concomitance of candidal antigen injection and the occurrence of vitiligo or hypopigmentation suggest a causal relationship in which immunotherapeutic antigen might either trigger a cytotoxic effect against melanocytes or induce Koebnerization (34, 35). In this study, no recurrence was observed among all cured patients that were treated with \textit{C. albicans} antigen injection during the follow-up period, which is in line with previous studies performed on common warts (9, 30, 36). Antigen intralesional immunotherapy enhances virus recognition by the host immune system with advantageous clearance of both treated and untreated lesions and diminished risk of future recurrence or appearance of new lesions (11, 29). The clearance of untreated genital warts, including nearby and distant internal genital lesions (which are usually difficult to reach and treat) was an important advantage of \textit{C. albicans} antigen immunotherapy reported in our study. This finding has also been reported by other investigators utilizing intraleral antigen immunotherapy for eradication of genital or non-genital warts (31, 32, 37). This could be attributed to the generation of widespread CMI attacking HPV as a response to antigen injection (30, 35).

It was proposed that intralesional antigen immunotherapy provokes proliferation of peripheral blood mononuclear cells and alteration in the T helper cells, favoring Th1 or Th2 responses with resultant activation of cytotoxic T cells and NK cells to eradicate HPV-infected cells (29, 35, 38). The release of various cytokines such as IL-2, IL-5, IL-8, IL-12, and IL-18 that induce a strong immune response against HPV has also been reported after intralessional antigen immunotherapy (30, 31).

Considering the oncogenic potential of some HPV strains affecting the genital area, an additional anti-oncogenic role of \textit{C. albicans} antigen immunotherapy might be suggested. Because of the immune-enhancing capability of recall antigens such as the \textit{C. albicans} antigen, which induces wart regression, some authors tried using it as a novel adjuvant to HPV therapeutic vaccine for biopsy-proven cervical intraepithelial neoplasia 2/3 (39, 40). Wang et al. (41) demonstrated significantly up-regulated CD40 and CD80 levels after \textit{C. albicans} antigen injection, indicating maturation effects of the peptide on Langerhans cells with secretion of IL-12 in addition to T-cell proliferation. In a recent study, \textit{C. albicans} antigen immunotherapy was found to induce a significant polarization of Th1 response with production of IFN-γ, which indicated that \textit{C. albicans} antigen may be used solely as a potential immunotherapeutic reagent not only for HPV-associated lesions but also for other viral infection or even cancers (39).

This study is mostly limited by the relatively small sample size and the relatively short follow-up period. Furthermore, histopathological as well as cytological evaluation of the lesions was not carried out, and it would be informative to conduct future studies using these maneuvers for evaluation of results and for detection of the effects of those treatment modalities in cases associated with dysplasia and carcinomas in situ.

Conclusions

PDL and \textit{C. albicans} antigen injection are simple, safe, and effective treatment alternatives for treatment of genital warts, even recalcitrant or multiple ones, with no post-procedural downtime and decreased risk of recurrence.

Although PDL resulted in much better cure rates, its cost, device availability, pain during the session, especially in massive large lesions, and difficult accessibility to internal genital warts might limit its use. \textit{C. albicans} antigen injection might be helpful for treating distant un.injected warts, including troublesome internal genital ones.

This study recommends trying \textit{Candida} antigen immunotherapy as an inexpensive and promising therapy in female patients with combined external and internal genital warts, in males with combined external and intraanal or intraurethral warts, and in children before resorting to other destructive interventions.

References


Galectin 1 in dermatology: current knowledge and perspectives

Efstathia Pasmatzi1 ✉, Christina Papadionysiou1, Alexandra Monastirli1,2, George Badavanis2, Dionyssios Tsambaos1,2

Abstract

Galectins are a family of soluble proteins that are widely distributed in nature and bind to a variety of glycoproteins and glycolipids bearing β-galactoside residues. They are involved in highly important processes at the molecular and cellular level in human cutaneous and extracutaneous tissues, and they exert biological effects of paramount importance through their interaction with cytoplasmic and nuclear proteins and the components of the cell surface and extracellular matrix. Galectin 1 (Gal 1), the first galectin isolated, is a noncovalent homodimeric protein with a 14 kDa monomer that contains one carbohydrate-recognition domain (CRD) and preferentially recognizes galactose-β1-4-N-acetyl-glucosamine sequences on N- or O-linked glycans. Gal 1 occurs intracellularly, extracellularly, and on the cell surface. In the last few years Gal 1 has emerged as a multifaceted protein that exerts a wide spectrum of regulatory effects in diverse normal and abnormal tissues and conditions, indicating a tremendous therapeutic potential. This review summarizes current knowledge on the expression of Gal 1 in normal and diseased human skin, its implications in the pathogenesis, diagnosis, and prognosis of cutaneous disorders, and the novel approach to the treatment of these disorders offered by the use of Gal 1 or its inhibitors/antagonists.

Keywords: galectins, galectin 1, epidermis

Introduction

One hundred thirty years ago, a protein discovered in castor bean extracts, was found to be capable of agglutinating animal erythrocytes (1). Since then, a considerable number of other proteins with agglutinating capacity have been found in various seeds and animals that are specific for binding to different glycans. All these agglutinins were termed lectins, from the Latin word legere ‘to select’ (2).

Today, it is known that lectins are proteins or glycoproteins of plant or animal origin widely distributed in nature that specifically bind to carbohydrate molecules or to carbohydrate functional groups of glycolipids and glycoproteins present in cell surfaces and also intracellularly (3).

Galectins constitute a family of β-galactoside-binding lectins that possess one or two unique structures termed “conserved carbohydrate-recognition domains” (CRDs), by means of which they bind with diverse carbohydrate ligands (4, 5). Nineteen mammalian galectins (13 in humans) have so far been identified (6), most of which consist of one CRD with a highly conserved amino acid sequence and a β-sandwich structure (characterized by two opposing antiparallel β-sheets), whereas a few others contain two homologous CRDs separated by a linker of up to 70 amino acids (4). Based on their structural properties, galectins can be classified into three major subfamilies:

1. The prototype, the largest subfamily, including galectins 1, 2, 5, 7, 10, 11, 13, 14, and 15, which contain one CRD;
2. The tandem-repeat type, including galectins 4, 6, 8, 9, and 12, which contain two distinct CRDs in tandem connected by a linker; and
3. The chimera type, including galectin 3, which consists of unusual tandem repeats of proline- and glycine-rich short stretches fused onto the CRD (5, 7, 8).

Galectins recognize β-galactose; however, the binding affinity of galectin subfamilies differs depending on the structure of glycocconjugates and the modifications of galactose residues, such as sialylation, fucosylation, and sulfation (5). Galectins are expressed both intracellularly and extracellularly, contain no classical signal sequence or transmembrane domain, and are secreted from the cells via nonclassical pathways (9). Galectins occur in various human cell types and tissues and in diverse mammals, fungi, nematodes, sponges, insects, and viruses. Many galectins are widely distributed in tissues, but few of them reveal a high tissue-specificity. Accumulating evidence suggests that galectins are involved in a wide variety of important molecular and cellular processes in both cutaneous and extracutaneous tissues.

This article summarizes current knowledge on the expression of galectin 1 (Gal 1) in normal and diseased human skin and on its potential functions and implications in the pathogenesis, diagnosis, prognosis, and treatment of cutaneous disorders. The overview of the available data is based on the results of an electronic literature research that was conducted on the Medline and Scopus databases through April 2018 using various combinations of the primary keyword galectins with relevant terms, the most important of which were keratinocytes, Langerhans cells, Merkel cells, melanocytes, lymphocytes, macrophages, skin, human adult epidermis, human embryonic epidermis, keratinization, infection, inflammation, immune response, cutaneous angiogenesis, melanoma, cutaneous neoplasms, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, actinic keratosis, xanthoma, nevi, Bowen's disease, tumor invasion, and metastasis.

Galectin 1

Gal 1, the first identified and best-studied prototypical member of the galectin family, is encoded in humans by the LGALS1 gene, which is located on chromosome 22 (q12) (10). It is a noncovalent homodimeric protein with a 14 kDa monomer that contains one CRD and preferentially recognizes galactose-β1-4-N-acetyl-glucosamine sequences on N- or O-linked glycans (11).
Gal 1 occurs intracellularly (in the cytoplasm and the nucleus), extracellularly, and on the cell surface (11).

Gal 1 is primarily released from the cells of adipose tissue, but it is also secreted by various other cell types. The cell types involved in the secretion and release of Gal 1 include human/porcine keratinocytes, thymic epithelial cells, fibroblasts, 3T3 cells, T- and B-cells, macrophages, dendritic cells, Langerhans cells, culturedstromal cells of human bone marrow, endothelial cells, and ovary cells (11–13). Various Gal 1 ligands are found on lymphocytes (CD7, CD43, and CD45), on endothelial cells (CD13, CD36, ROBO4, and integrins), and in the extracellular matrix (fibronectin, integrins, laminin, ROBO4, and GM1) (14).

The most important biological properties and actions of this galectin include involvement in morphogenesis, angiogenesis, regulation of the cell cycle, proliferation and immune response, cell-cell and cell-matrix adhesion, apoptosis, inflammation, tumor invasion and metastasis (10, 11, 15–19), regulation of the innate and the adaptive immune response (20), promotion of the subsidence of autoimmune inflammation and suppression of allergen-induced inflammation and antibacterial immune response (21), contribution to the induction of B cells’ regulatory function (22) and to the escape of tumor cells from immune surveillance (21), involvement in tumoral angiogenesis, hypoxia and metastasis (23), and the mechanisms of microglial modulation, polarization, and remyelination (24).

Normal human skin

Gal 1 has been detected by Western blotting in human embryonic skin protein extracts with increasing amounts from 10 weeks to 14 weeks (estimated gestational age, EGA). Immunohistochemistry revealed no reactivity in fetal epidermal cells of 11-week EGA embryos, whereas connective tissue cells and dermal extracellular matrix were weakly positive for Gal 1 (25). At a later stage of epidermal morphogenesis (14-weeks EGA), basal epidermal cells revealed expression of Gal 1, whereas cells from the upper epidermal layers and the developing follicular buds remained negative for this galectin (25). These findings could be interpreted in terms of possible Gal 1 involvement in the regulation of keratinocyte proliferation.

In adult human skin, expression of Gal 1 has been found in the cytoplasm of keratinocytes in all layers of normal epidermis (13, 26–28), as well as in hair follicles and in the extracellular matrix of the dermis (26, 29). Furthermore, Gal 1 has been found in both the nucleus and the cytoplasm of normal fibroblasts and Langerhans cells (13) and in the cytoplasm of human epidermal melanocytes (10).

Because Gal 1 stimulates the maturation and migration of human dendritic cells, it has been suggested that it may contribute to the initiation of cutaneous immune response (30, 31). It has been shown that this galectin is capable of mediating cell-matrix interactions that are of essential importance in cell migration, re-epithelization, and wound healing (32, 33). Moreover, Dvoranikova et al. (34) reported that Gal 1 can induce both the conversion of dermal fibroblasts into myofibroblasts and the production of extracellular matrix.

Cutaneous and systemic disorders

A. Psoriasis

In contrast to the keratinocytes in all layers of normal human epidermis that express Gal 1, those of the lesional psoriatic epidermis reveal no cytoplasmic and/or nuclear immunoreactivity (27). It therefore seems reasonable to suggest that the lack of Gal 1 expression in psoriatic epidermis could be associated with the abnormal keratinization and/or increased proliferation of keratinocytes in psoriatic lesions. Interestingly, a downregulation of the expression of this galectin was found in Langerhans cells and dendritic cells derived from the skin lesions of psoriatic patients, as compared to those of healthy controls (35), whereas large amounts of Gal 1 were found in the extracellular matrix of psoriatic dermis (27).

B. Atopic dermatitis

Interactions between immune dysregulation, genetic predisposition, impaired skin barrier, and bacterial and environmental factors are thought to be involved in the complex pathogenesis of atopic dermatitis, which still remains obscure (36, 37). Better understanding of the pathogenic mechanisms would greatly contribute to the identification of molecules and pathways responsible for the development of atopic dermatitis, which could serve as novel targets for its treatment.

In view of the multifaceted immunoregulatory properties of Gal 1, Correa et al. (38) evaluated the possible therapeutic efficacy of intraperitoneally applied recombinant Gal 1 on an ovalbumin-induced atopic dermatitis model in BALB/c mice. In Gal 1–treated mice they found that Gal 1 was as effective as dexamethasone in causing clinically evident improvement of skin lesions, reduction in local eotaxin and interferon-gamma levels, suppression of eosinophil and mast cell infiltration, decrease of interleukin 17 plasma levels, activation of signal-regulated kinase, and down-regulation of endogenous Gal 1. These very interesting findings indicate that the use of Gal 1 may represent a novel and promising approach to the treatment of atopic dermatitis, which is presently far from satisfactory.

Cutaneous neoplasms

A. Epithelial

The expression of this galectin has been extensively studied only in squamous cell carcinomas (SCCs) of the oral cavity and of the head and neck. In the healthy oral mucosa tissue, all epithelial cells were devoid of Gal 1 immunostaining except those of the basal layer (39). A weak nuclear or cytoplasmic expression of Gal 1 was demonstrated in both the oral papilloma and the oral SCC, indicating that this galectin is not differentially expressed in benign and malignant oral tissue (40). Strong Gal 1 immunostaining was detected in early-stage oral SCC, being primarily localized in stromal cells, including fibroblasts, plasma cells, and giant cells. In late-stage oral SCCs, negative staining of Gal 1 was detected in the well-differentiated intermediate layer of carcinoma cells.

Gal 1 immunoreactivity was exclusively found in the less-differentiated cells around carcinomatous clusters, as well as in stromal plasma cells and fibroblasts (39).

During the metastatic stage, the only significant immunoreactivity was found in carcinoma cells at the tumor invasion front (39). Based on their findings, these authors suggested that Gal 1 may represent a novel molecular target for the diagnosis and prognosis of oral SCCs, and that its inhibitors might be useful in the management of early-stage oral carcinogenesis. More recently
Noda et al. (41) determined that Gal 1 expression in gingival SCC significantly correlates with the histological differentiation of tumor cells, the extent of apoptosis and T cell infiltration, lymph node metastasis, and overall survival rate. Based on their findings, these authors suggested that this galectin may be used as a clinicopathological prognostic marker for gingival SCC.

In a thorough study, Valach et al. (42) found that upregulation of Gal 1 expression in head and neck SCCs significantly correlates with a) the presence of cancer-associated stromal myofibroblasts and b) the activation of genes linked to poor prognosis factors of head and neck SCCs, such as upregulation of nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) and splicing downregulation. Noda et al. (43) reported a high sensitivity and specificity of Gal 1 immunoreactivity in the detection of neoplastic cells in tissue specimens and smears derived from oral SCCs, and they suggested that this galectin may be a useful immunochemical marker for oral SCCs.

Because Gal 1 is a hypoxia-regulated protein and a prognostic marker in head and neck SCC, Koounce et al. (44) investigated the antitumor potential of a low molecular weight and non-peptidic Gal 1 inhibitor (OTX008) in athymic nude mice inoculated with two different cell lines from human head and neck SCCs. They found that OTX008 induced tumor cell normalization and inhibited tumor growth without any apparent toxicity. In view of these promising results, they suggested that the clinical application of OTX008 or other Gal 1 inhibitors may represent a novel approach to the treatment of head and neck SCCs. Interestingly, this inhibitor is also capable of directly and indirectly affecting cell cycle and survival and angiogenesis (6). Moreover, its in vitro and in vivo efficacy has been proven in several studies either as monotherapy or in combination with other regimens (45–47).

B. Melanomas

Gal 1 is highly expressed in melanomas; however, its immunoreactivity in these tumors is not associated with the overall or disease-free survival of the patients (10). This galectin is secreted by melanoma cells, exerting distinct stimulatory effects on their migration and also on angiogenesis (48, 49). Furthermore, it protects melanoma cells from the cytotoxic effects of chemotherapy and radiotherapy, and it assists them in escaping from immune surveillance mechanisms through induction of apoptosis of tumor-specific activated T cells attacking the melanoma (49, 50). In view of these properties and actions of Gal 1, it can be suggested that this galectin may be used as a novel molecular target in the treatment of melanoma because the reduction of its expression or its deletion could result in the loss of the immune privilege of malignant cells and in a marked decrease in both the resistance of this tumor to chemotherapy and radiotherapy and its metastatic potential (49). This hypothesis is supported by the findings of two more recent studies.

First, Yazawa et al. (51) studied the expression, identity, and function of the ligands of Gal 1 in the progression of melanoma and found an abundance of Gal 1 ligands in primary and metastatic melanoma that is lacking in epidermal melanocytes of normal human skin or the apparently normal skin surrounding the melanoma and in benign nevi. Furthermore, they demonstrated that the melanoma cell adhesion molecule (MCAM), which is implicated in the development of the tumor, was a major Gal 1 ligand. Interestingly, when MCAM-silenced melanoma cells were grown in mice deficient in Gal 1, melanoma growth was markedly reduced.

Second, Wu et al. (52) reported that in a subgroup of melanoma patients treated with ipilimumab and bevacizumab there was an increase in the serum levels of Gal 1 that was related to a decrease in survival. Interestingly, a different subgroup of melanoma patients revealed an enhancement of humoral immune response to Gal 1 that was associated with a favorable clinical outcome. Thus, these authors suggested that the levels of circulating Gal 1 and Gal 1 antibodies may be of importance for the efficacy of combined ipilimumab and bevacizumab treatment of melanoma and may represent a potential biomarker for immune therapy for melanoma.

In view of all these findings and the immunosuppressive, proangiogenic, and tumorigenic potential of Gal 1 (53), it seems reasonable to assume that this galectin alone or combined with immune checkpoint blockade may represent a significant therapeutic target and that the use of Gal 1 inhibitors/antagonists may indeed open a new and promising approach to the treatment of melanoma.

C. T cell lymphomas

In the lesions of patients with patch and tumor stage mycosis fungoides (MF), Gal 1 immunoreactivity is found in both the dermis and the epidermis in close proximity to infiltrating lymphocytes and Sézary cells, which exhibit strong expression of this galectin on their surface, whereas keratinocytes are negative. In the dermis, expression of Gal 1 is observed in scattered fibroblasts, endothelial cells, and macrophages (54).

It is known that Gal 1 can induce caspase-independent apoptosis of T cells and consequently suppression of T cell immunity (55). However, the susceptibility of T cells to Gal 1-induced apoptosis requires the expression of specific glycoprotein receptors on their surface, such as CD7 (56), containing the specific oligosaccharides that are recognized by Gal 1 (54). Thus, loss of CD7 expression on the surface of Sézary cells and alteration of their glycosylation (characterized by the occurrence of sialylated core 1 O-glycans) most probably contribute to the resistance of these cells to a variety of apoptosis-inducing agents, including Gal 1, and to the poor prognosis of T cell lymphoma (54). Interestingly, Rappol et al. (57) showed that the resistance of CD7–Sézary cells to Gal 1–mediated apoptosis may not only represent a mechanism of their immune escape but could also explain their progressive accumulation in the skin, peripheral blood, and other tissues of patients with Sézary syndrome. It may be suggested, therefore, that genes regulating glycosylation may be used as molecular targets for the development of novel compounds for the treatment of cutaneous T cell lymphomas (CTCLs) through enhancement of the susceptibility of malignant cells to apoptosis.

Cedeno-Laurent (58) reported that clonal malignant T cells in patients with advanced-stage (3 or 4) CTCLs reveal a Th2 cytokine pattern and strong intracellular Gal 1 expression. Moreover, plasma Gal 1 levels were increased in patients with leukemic CTCLs (L-CTCLs) as compared to healthy controls, and conditioned supernatants from primary L-CTCLs cell cultures caused a marked impairment of normal T-cell proliferation and a downregulation of Th1 responses in a β-galactoside–dependent manner, leading to impaired antitumor responses and increased susceptibility to infection. Based on their findings, these authors suggested that neutralization of Gal 1 interactions with its ligands may represent an effective approach to the augmentation of antineoplastic immune response in patients with L-CTCLs.
Miscellaneous: wounds and scars

Gal 1 is expressed in human mesenchymal stem cells, acts as an autocrine negative growth regulator of fibroblasts, and is capable of inducing marked extracellular matrix formation and transforming growth factor beta (TGF-β)–independent conversion of fibroblasts into myofibroblasts (34).

In a comparative study using proteomic analysis, Ong et al. (59) found a significant increase of Gal 1 expression in keloid scars (KS) as compared to normal skin. In addition, Gai et al. (60), in an experimental study on skin wound healing using Sprague Dawley rats, found an increase in the expression of Gal 1 during the early phases of re-epithelialization followed by a significant decrease thereafter, indicating that this galectin may play a significant role in the early phases of wound healing and contraction.

In a recent experimental study, Lin et al. (61) investigated the role of this galectin in cutaneous wound healing using Gal 1 knockout mice. They found that Gal 1 induced the activation, migration, and proliferation of myofibroblasts, accelerated the healing of wounds, and decreased the mortality of diabetic animals with cutaneous wounds. Taken together, the findings of these studies suggest that Gal 1 could be used in the development of a novel approach to the prevention of and/or therapy for cutaneous wounds.

Conclusion

Galectins are a family of small and highly conserved lectins that are widely distributed in nature. They bind to a variety of glycoproteins and glycolipids bearing β-galactoside residues and interact with diverse non-glycosylated molecules within the nucleus and the cytoplasm.

Gal 1, the first identified and best-studied prototypical member of the galectin family, is involved in a wide variety of biological processes in cutaneous and extracutaneous tissues.

In normal adult human skin, Gal 1 is expressed in the cytoplasm of keratinocytes in all epidermal layers, hair follicles, the extracellular matrix of the dermis, normal fibroblasts, Langerhans cells, and human epidermal melanocytes. Abnormalities in their expression are associated with various cutaneous disorders and are thought to be involved in the pathogenic mechanisms of these disorders.

Recent studies have shown that Gal 1 may be regarded as a useful diagnostic and prognostic factor in oral SCCs and that its administration may represent a novel and effective approach for the treatment of atopic dermatitis and cutaneous wounds. Accumulating experimental and clinical evidence strongly suggests that selective inhibition of this galectin or its interactions with its own ligands may open up entirely new avenues in the treatment of cutaneous neoplastic disorders and may provide a more thorough understanding of and greater insight into the mechanisms of their pathogenesis and also into the processes underlying the biological function of Gal 1 (Fig. 1).

Dedicated to the memory of Ourania Marselou-Kinti.

Figure 1 | Positive effects and potential therapeutic targets of Galectin 1 (Gal 1) and Gal 1 inhibitors. SCC = squamous cell carcinoma.

References

Galectin 1 in dermatology


Kožna obolenja, ki se odzivajo na lokalno zdravljenje s kortikosteroidi
Močna učinkovitost z varnostnim profilom blagega steroida

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Locoidon™ lipocrema 1 mg/g krema

1 g kreme vsebuje 1 mg hidrokortizonbutirata

Uravnoteženo razmerje med oljno in vodno fazo (posebej primerna za suho kožo, ki se lušči)

Terapevtske indikacije

• kontaktni ekcem (akutni, subakutni, kronični);
• dermatitis: navadni, detrivni, atopijski, solarni, toksični, hipostatični, intertriginozni,
diseboroični, antimikotiki;
• psoriasis;
• lichen ruber planus;
• kronični eritematodes;
• vzdrževalno zdravljenje dermatoz, ki so bile predhodno zdravljene z močnejšimi kortikosteroidi.

Odmerjanje in način uporabe

Zdravilo Locoidon lipocrema ima uravnoteženo razmerje med oljno in vodno fazo, kar učinkuje na kožo osvežilno in jo zmehča. Posebej je primerna za suho kožo, ki se lušči. Zdravilo Locoidon lipocrema ima uravnoteženo razmerje med oljno in vodno fazo, kar učinkuje na kožo osvežilno in jo zmehča. Posebej je primerna za suho kožo, ki se lušči.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Neželeni učinki

Locoidon™ lipocrema nanašamo dvakrat na dan, pri resnejših pa lahko do štirikrat na dan, vendar mora o tem odločati zdravnik. Za majhne otroke običajno zadošča nanos zdravila nanašamo na obolelo kožo in ga vanjo narahlo vtremo. Pri blažjih oblikah obolenj medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.

Medsebojno delovanje z drugimi zdravili

Podobna opašalca in preobčutljivost

Pri ulcerativnih in glikolitičnih oblikah lahko zdravljenje kombiniramo z antibakterijski ali antimikotiki. Pri uporabi zdravila na velikih površinah kože, v večjih količinah ali na občutljivih mestih in pod okluzivnim povojem ali lokem hidrokortizonbutirat absorbira skozi kožo in premoča občutljivost kožnih tkiv.
Trichotillomania: a psychopathological perspective and the psychiatric comorbidity of hair pulling

Sarah Anwar¹, Mohammad Jafferany²,³

Abstract

Trichotillomania, or hair-pulling disorder, is classified as an obsessive-compulsive spectrum disorder and is seen predominantly in females. This is a non-systematic review article focusing on the psychopathological features of hair pulling. It is speculated that hair pulling may function to provide short-term relief from stress and other unwanted emotional states, thus serving as a method of emotion regulation. The prevalence of trichotillomania ranges from 1 to 3%. The most targeted site is the scalp, and other common areas include pubic hair and facial regions such as the eyebrows, eyelashes, and beard. Individuals suffering from this disorder tend to avoid social environments due to embarrassment regarding their appearance and fears of being judged by peers. Trichotillomania is associated with significant functional impairment and increased risks of comorbid psychiatric disorders such as other body-focused repetitive behaviors, depression, anxiety, and addictive disorders. This article reviews the epidemiology, clinical features, diagnostic criteria, and psychopathology of trichotillomania with an emphasis on psychopathology and psychiatric comorbidity.

Keywords: trichotillomania, hair pulling, psychodermatology, psychopathology

Introduction

Trichotillomania, or hair-pulling disorder, is classified as an obsessive-compulsive spectrum disorder. It involves repeated urges to remove one’s body hair, resulting in hair loss. Hair-pulling behavior is often preceded by feelings of distress and results in temporarily relief (1). However, the revised diagnostic criteria as set by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders has removed the feelings of gratification (2). The most common sites reported are the scalp, eyelashes, eyebrows, beard, and pubic hair (3). Hair pulling often involves one or more body areas and may take place for consecutive hours or shorter intervals that appear throughout the day. Pulling generally occurs when alone as opposed to social environments, and many studies have demonstrated that the vast majority of those suffering from trichotillomania report feelings of unattractiveness, humiliation, and low self-confidence (4).

Trichotillomania is often associated with significant distress and functional impairment. Many that suffer from this condition feel embarrassed about their hair loss and tend to avoid social situations due to fear of being judged by their peers (5). Overall, hair pulling may create a cycle in which stress and other undesirable emotions that accompany the hair loss directly correlate with urges to pull the hair and, consequently, a decrease in quality of life. Recent studies have led to the identification of two distinctive hair-pulling styles, automatic and focused. Automatic pulling occurs with little or no awareness. Many that participate in automatic pulling are unaware of this behavior until they are faced with unwanted consequences such as a new bald spot or handful of hair (6). Conversely, individuals that engage in focused pulling tend to be aware of this activity and may pull to reduce stress or for temporary feelings of pleasure that may accompany the pulling behavior. Most that suffer from trichotillomania have been shown to engage in both automatic and focused pulling (7).

Epidemiology

Although few epidemiological studies of trichotillomania exist, recent community findings have estimated the life prevalence of this condition to be between 1 and 3%, with a significant female predominance (8). However, disagreements exist regarding the exact sex ratio because some studies suggest that women dominate 9:1 for this disorder whereas others suggest that the sex ratio is actually closer to 4:1 (4). However, the sex distribution in children has been found to be almost identical (9).

Although little information is available on the physiological developments associated with trichotillomania, the presence of a familial component has been identified, with approximately 34.8% of patients reporting a family history of trichotillomania (10). Multiple findings have demonstrated an increased risk of trichotillomania in first-degree relatives as well as greater risks for accompanied anxiety disorders and other body-focused repetitive behaviors. A recent family study has confirmed that first-degree relatives of patients have increased risks for repeated hair-pulling behavior (11). Moreover, a significant proportion of individuals with trichotillomania have another current psychiatric diagnosis or another lifetime (present and/or past) psychiatric diagnosis. Specifically, trichotillomania showed substantial overlap with depressive, anxiety, addictive, and other body-focused repetitive behavior disorders.

Clinical features

The average age of onset for trichotillomania is 12, with this disorder most commonly first seen between ages 10 to 13 (12). Hair pulling generally takes place in one or more areas, with the most common
site being the scalp, and other popular regions being pubic hair and facial hair such as the eyebrows, eyelashes, and beard (6). Recent studies suggest that children develop more focused pulling and pull from an increasing number of regions as they become older (9).

Trichotillomania is most frequently seen in females, who also face other body-focused repetitive behavior disorders such as nail biting, cheek biting, and skin picking (3). In addition, patients tend to experience comorbid psychiatric conditions such as depressive, anxiety, and addictive disorders at a significant rate (9). Post-pulling behavior varies among individuals. Whereas some discard the hair after it has been removed, others are known to engage in various activities with the removed hair, ranging from examining, playing with, biting, and even swallowing it. Recent research has demonstrated that over 20% of trichotillomania patients ingest their hair, a practice that can lead to the creation of masses of hair, or trichobezoars, causing undesirable medical issues (13).

Individuals with trichotillomania often experience feelings of stress and embarrassment due to the resulting hair loss. Many avoid social situations because they are very conscious of unwanted characteristics of hair pulling such as bald spots, and they fear judgement from others (7). Hair pulling generally occurs when alone or performing a sedentary activity, and it can form a vicious cycle in which the negative emotions associated with post-pulling encourage continued pulling in hopes of temporary relief (1). Those suffering from this condition face significant risks of anxiety and depression, and almost one-third report a low or very low quality of life (5).

Diagnostic criteria

According to the DSM-5, the current diagnostic criteria for trichotillomania are as follows: i) recurrent pulling out of one’s hair, resulting in hair loss; ii) repeated attempts to decrease or stop hair pulling; iii) the hair pulling causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; iv) the hair pulling or hair loss is not attributable to another medical condition (e.g., a dermatological condition); and v) the hair pulling is not better explained by the symptoms of another mental disorder (e.g., attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder) (2). Trichotillomania appears in the ICD-10, in Chapter 5 on mental and behavioral disorders, and it is coded as F63.3.

Few individuals with trichotillomania obtain professional help. Many are unaware that hair pulling is not an uncommon psychiatric condition, feel embarrassed about their appearance, or worry that an effective treatment does not exist. However, with treatment, only about 14% of adults experience any decrease in symptoms (3).

A diagnosis of trichotillomania is typically made from a psychiatric examination when hair-pulling behavior is suspected or a patient confesses to removing his or her own hair. Any comorbid conditions are also considered, and treatment options are evaluated. However, additional medical testing becomes necessary if a patient admits to ingesting his or her own hair because this activity can lead to the formation of trichobezoars and further medical concerns (7).

Trichoscopy, an examination of hair and scalp regions using a dermatoscope, is a common technique used to identify hair-pulling behavior. Trichotillomania patients often present asymmetric regions of alopecia in addition to fractured, coiled, and short vellus hairs. Sparse yellow dots that sometimes contain remnants of dead hair follicles presenting as black dots also point to a diagnosis of trichotillomania (14).

Psychopathology

It is speculated that hair pulling may serve as a means to release the tension that is generated by various emotional states (1). Pulling may provide temporary relief from negative emotions such as shame, sadness, frustration, anger, anxiety, and boredom. Multiple studies monitoring emotion regulation in individuals with trichotillomania have demonstrated that these individuals struggle to regulate various emotional states when compared to controls (19). Thus, the development of trichotillomania may be a potential behavioral response in order to cope with unwanted negative emotions. Many findings have revealed that decreases in feelings of boredom, stress, and frustration have been seen across the pulling cycle. In addition, temporary increases in pleasure and relief have been found. However, patients have reported increased feelings of shame, sadness, and frustration shortly after hair pulling was finished (16). These data support the idea that pulling may function to reduce unwanted emotions and is thus reinforced, although any feelings of relief are temporary and often result in the previous unwanted emotions, thus creating a vicious cycle.

Trichotillomania patients are known to suffer from comorbid mental disorders at a much greater rate than the general population (6). A recent study on 85 participants revealed that 38.8% (33 patients) had at least one other current psychiatric disorder and 78.8% (67 patients) had at least one other lifetime disorder. Depression, anxiety, mood, and addictive disorders were most frequently presented in this study (17). However, while research concerning the numerical presence of comorbid conditions has been consistent, there have been discrepancies regarding the frequency of specific conditions. A clinical sample demonstrated that 28.6% of patients suffered from major depression and 10.7% experienced obsessive-compulsive disorder (OCD), although previous studies have documented higher rates of both comorbid conditions (7). In addition, it has been reported that approximately 70% of individuals face another body-focused repetitive disorder such as skin picking or nail biting (18).

Differences in the frequency of hair-pulling urges and pulling styles as children age indicate that trichotillomania may follow a developmental progression. Children are known to face more urges to pull and spend more time pulling as they get older (9). However, this positive correlation between age and pulling solely involves focused pulling. It is speculated that children become more aware of pulling urges as they become older. However, it is uncertain whether children face increased urges as they age or are more likely to recognize these urges. Multiple studies have considered a relationship between ages of biological changes in both children and adults with increases in focused pulling and functional impairment (8). These findings indicate that the reason behind increased pulling urges as children age is the onset of puberty. Similarly, adult women have been seen to experience more significant pulling urges during the years that directly precede menopause, further supporting the claim that biological changes may be associated with focused pulling (19).

Recent findings reveal that personality traits may serve as a predictive factor for a trichotillomania diagnosis as well as pulling intensity and styles. A strong correlation was demonstrated...
between neuroticism and a trichotillomania diagnosis with each one-point increase in neuroticism scores serving as a 10% higher chance of a diagnosis. Higher neuroticism was also linked to stronger pulling intensity and increased focused pulling (20). No relation between the other NEO traits and a diagnosis has been found, and none of the traits predicted automatic pulling. However, higher openness and lower agreeableness are also known to be related to greater pulling intensity, and lower openness is associated with more focused pulling (21).

The relationship between childhood trauma and violence has been a subject of interest in recent years, and one study has demonstrated that 91% of patients experienced trauma or violence at some point throughout their lives. The vast majority of these episodes involved familial abuse ranging from verbal abuse to physical and sexual assault. Furthermore, 86% of these individuals believed that their traumatic experiences were related to their first memories of pulling because the hair-pulling behavior occurred within a year of the violent episodes in each case (22). These patients faced significant childhood trauma, suggesting that distressing experiences may play a role in the development of trichotillomania. Other studies have shown that approximately 76 to 86% of patients have experienced at least one traumatic life event and 19% have comorbid post-traumatic stress disorder (PTSD), which is an occurrence much greater than that found in the general population. However, a decrease in PTSD symptoms has been observed with a prolonged duration of trichotillomania (10). Thus, trichotillomania may serve as a means to allow patients to cope with disturbing thoughts regarding previous traumatic events.

A high comorbidity of trichotillomania, pathologic skin picking, and OCD has been found, and these behaviors have been labeled as grooming disorders in a recent family study due to their overlap in characteristics of repetitive behaviors. The rates of both trichotillomania patients with comorbid OCD and OCD patients that suffer from trichotillomania are higher than those found in the general population, and it has since been speculated that grooming disorders may occupy a subgroup of OCD (23). Although limited research exists on the relationship between OCD and trichotillomania, it is believed that about 5 to 30% of trichotillomania patients suffer from OCD, with a recent study stating this value to be 18.9% (24). Similarly, approximately 5 to 7% of individuals with OCD are known to experience trichotillomania (25).

Trichotillomania is often associated with depressive, anxiety, and addictive disorders in adults. Recent studies exploring the relationship between depressive and anxiety disorders in children have discovered that almost 50% of children experience symptoms of depression or anxiety. The findings from one study demonstrate that children that develop trichotillomania later in childhood tend to exhibit an increased number and intensity of depressive symptoms. In this sample, approximately 50% of teenagers faced significant feelings of depression compared to only 17% of younger children exhibiting depressive symptoms (9). It has been hypothesized that those with a later onset of trichotillomania, specifically teenagers, are more embarrassed about hair loss and receiving judgment from peers, whereas those with an earlier onset may have developed techniques to avoid feelings of shame or may be better able to conceal their trichotillomania from others (8). In addition, a positive correlation has been shown between worse trichotillomania symptoms and more intense depressive symptoms (17).

Recent research suggests that sex may also be a critical clinical aspect of identifying and treating trichotillomania. Although the demographics of men and women with this disorder tend to be remarkably consistent, there is little agreement on differences in age of onset, functional impairment, and rates of comorbidity (19). Although some findings indicate that men have a later age of onset, report higher levels of functional impairment, and have similar comorbidity as women, more recent findings suggest that age of onset, number of pulling sites, and time spent pulling does not vary between the sexes, but females report greater functional impairment and experience greater psychiatric comorbidity (8).

**Treatment**

Although no FDA-approved medication for trichotillomania currently exists, habit reversal therapy in combination with pharmacological treatment has demonstrated promise. Habit reversal therapy sessions generally occur weekly and involve self-monitoring, awareness and prevention training, and stimulus control techniques. Although this form of treatment was often accompanied by anti-depressants and anti-psychotics in the past, N-acetyl cysteine has since gained recognition for its effectiveness in treatment for adults with trichotillomania (26). Swedo et al. reported that clomipramine appears to be effective in the short-term treatment of trichotillomania (27). Trichotillomania has also been successfully treated with risperidone and naltrexone in a geriatric case report (28). Other potential non-pharmacological treatments include psychoanalysis, cognitive-behavioral therapy, acceptance and commitment therapy, and dialectical behavioral therapy (29).

**Conclusion**

Trichotillomania is a psychodermatological condition associated with hair-pulling behavior that is seen predominantly in women. Individuals with this disorder tend to face significant functional impairment and are known to suffer from comorbid disorders such as other body-focused repetitive behaviors, depression, anxiety, and addictive disorders at significant rates.

Hair pulling may offer temporary relief from undesirable feelings, thus serving as a method of emotion regulation. Many patients were victims of childhood trauma and violence, and it is believed that the development of trichotillomania may provide a technique to manage intrusive thoughts pertaining to traumatic events. Although habit reversal therapy is the mainstay of treatment, newer pharmacological treatments such as N-acetyl cysteine are being tried with variable results. Selective serotonin reuptake inhibitors, mood stabilizers, and antipsychotic medications have also been successful in some case reports and open label trials. Collaboration between psychiatrists and dermatologists is crucial in the diagnosis and treatment of trichotillomania in patients.
References

Successful treatment of extensive uremic calciphylaxis with intravenous sodium thiosulfate and its potential in treating various diseases of pathologic calcification

Sandra Burja1,2, Alen Jovic3, Robert Ekart1,3, Nejc Piko4, Jovan Miljkovic1, Vesna Breznik2

Abstract
A 72-year-old female patient presented with an end-stage renal disease on- line hemodiafiltration and warfarin treatment with advanced ulcerated calciphylaxis on the lower extremities, complicated by two episodes of cellulitis. She was successfully treated for 8 months with intravenous sodium thiosulfate in combination with modification of medication and dialysis treatment, careful wound care, and other supportive measures. Calciphylaxis is an uncommon life-threatening systemic disease, mostly occurring in patients with chronic kidney disease and other risk factors. Vascular calcifications and inflammation lead to thrombotic occlusions of the cutaneous and subcutaneous arterioles, which provoke livedoid painful plaques with possible progression to necrotic ulcers. Conventional treatment is supportive. In recent decades, off-label treatment with sodium thiosulfate, a potent calcium chelator, antioxidant, and vasodilator, has been increasingly reported to be highly efficient in calciphylaxis, leading to significantly lower mortality rates. Knowledge of advancement in the treatment of calciphylaxis, which was previously a highly fatal disease, is important for physicians and other professionals from various medical fields.

Keywords: calciphylaxis, hemodialysis, chronic kidney disease, sodium thiosulfate, multimodal, wound care

Introduction
Calciphylaxis or calcific uremic arteriolopathy is a severe complication of advanced chronic kidney disease (CKD) and other risk factors, including female gender, Caucasian race, obesity, diabetes mellitus, systemic autoimmune and liver diseases, elevated levels of calcium-phosphate product, hypercoagulable diseases, and therapy with calcium and vitamin D analogues, warfarin, corticosteroid drugs, and immunosuppressive drugs (1).

It is uncommon, occurring in 1 to 4.5% of patients on renal replacement therapy (2). The pathogenesis is poorly understood. Calcium and phosphorous imbalance are considered to provoke calcification of small and medium-sized arterioles in the dermis and subcutaneous tissue, leading to mural inflammation, thrombosis, fibrosis, and ischemia. Clinically, it presents with tender erythematous papules, nodules, and plaques. Gradually, it progresses into a livedoid and stellate pattern with possible necrosis and extremely painful ulcers, predisposing the patient to infections and sepsis (3–6).

The treatment conventionally consists of local wound management, correction of risk factors, and correction of factors that delay healing, such as infection, anemia, and hypoxia. The reported mortality is 50 to 80% after 1 year and is due to infection, organ failure, severe pain, and adverse effects of treatment (7–9).

Case report
A 72-year-old female patient presented with necrotic ulcers on both shins and thighs, developing into large livedoid subcutaneous plaques. The skin lesions were progressively increasing in size and pain, rating 9/10 on the visual analog scale (VAS) for 1 to 2 months (Fig. 1). She had an end-stage renal disease (ESRD) on treatment with on-line post-dilution hemodiafiltration (HDF) for 5 years, secondary hyperparathyroidism, chronic atrial fibrillation, ischemic heart disease with past myocardial infarction, dyslipidemia, asthma, osteoporosis, depression, and a past venous ulcer of the right leg. Her medications included warfarin, carvedilol, perindopril, methylidigoxin, sevelamer, cinacalcet, tizanidine, rosuvastatin, pantoprazole, sertraline, bromazepam, tramadol, and paracetamol.

On admission several laboratory values were outside the normal range (reference ranges in brackets): C-reactive protein 38 mg/l (< 5), erythrocyte sedimentation rate 72 mm/h (< 10), creatinine 426 µmol/l (49–90), gamma-GT 4.7 µkat/l (< 0.63), urea 10.1 mmol/l (2.8–7.5), S-sodium 133 mmol/l (135–145), S-potassium 6.0 mmol/l (3.5–5.3), S-chloride 95 mmol/l (97–110), S-phosphate 1.6 mmol/l (0.84–1.45), and intact parathyroid hormone 188.9 ng/l (15–65). The findings for serum calcium, albumin, anti-nuclear antibodies,
extractable nuclear antigen panel, cryoglobulins, complement C3 and C4, rheumatoid factor, antiphospholipid antibodies, protein C, and protein S were normal. No mutation of the Leiden V factor was found. Duplex ultrasound showed insufficiency of the small saphenous vein and great saphenous vein branches on the right shin and insufficiency of the great saphenous vein on the distal part of the left shin. Severe calcinosis of the arteries was noted. However, no hemodynamically significant stenosis of lower extremity arteries was detected. Radiographic imaging of both shins demonstrated moderate skin calcifications (Fig. 2). A 4 mm punch biopsy was taken from the margin of the leg ulcer and sent for histopathological examination, which confirmed the diagnosis of calciphylaxis (Fig. 3).

Initial management included discontinuation of therapy with warfarin and initiation of low-molecular-weight heparin therapy. The dose of sevelamer and cinacalcet was modified according to the levels of serum calcium, phosphate, and parathyroid hormone. HDF sessions were prolonged, and a dialysate with low calcium concentration (1.25 mmol/l) was used. High-flow oxygen therapy (10 l/min of oxygen through a 40% Venturi mask for 90 minutes daily) was administered. The pain was initially addressed with metamizole and oxycodone, which were later exchanged for a bu- prenaline transdermal patch. Due to the burning character of the pain, pregabalin was added. Off-label treatment with sodium thiosulfate (STS) was initiated with one intralosomal application of STS (10 ml of 250 mg/ml STS solution was injected into calcified plaques on the patient’s right shin). Afterward, intravenous treatment with STS was implemented (25 mg of STS diluted in 100 ml of 0.9% sodium chloride intravenously during the last 60 minutes of every HDF session, three times weekly). After 3 weeks (nine applications of intravenous STS), a significant improvement of the skin lesions and a decline in laboratory inflammatory parameters and pain (VAS 3/10) were noted.

Two weeks after admission, the patient developed clinical and laboratory signs of cellulitis on her right shin. Empirical oral therapy with amoxicillin/clavulanic acid in combination with ciprofloxacin was initiated after consultation with an infectologist. Due to worsening of local status, it was changed after 6 days for intravenous antibiotic therapy with piperacillin/tazobactam according to wound swab results (Escherichia coli, Enterococcus faecalis and faecium, Klebsiella pneumoniae, and Achromobacter sp.) and continued for 14 days. Three months after admission, the cellulitis on her right shin recurred and responded to treatment with intravenous amoxicillin/clavulanic acid for 14 days.

Careful local wound care was performed by skilled doctors and nurses from the dermatology department: cleaning with antiseptic soaps and solutions; autolytic debridement with hydrogels; hydrocolloid and silver alginate dressings; conservative sharp debridement of necrotic tissue by using a scalpel, scissors, and curette; and compression with long- and later short-stretch bandages due to accompanying edema. After 8 months of multidisciplinary management, complete healing of the leg ulcers was achieved (Fig. 4). Significant improvement in the patient’s physical and psychological condition was observed during treatment. At the last follow-up 5 months after the healing of all ulcers, the patient had no signs of calciphylaxis.
Discussion

Deposition of insoluble calcium salts in the tissue, cutaneous calcinosis (CC), can be caused by various diseases. It is divided into five types: dystrophic, metastatic, idiopathic, and iatrogenic CC, and calciphylaxis (10). The most severe form of CC is calciphylaxis, which is an obliterative vasculopathy that causes ischemia and necrosis of the skin, subcutaneous fat, and other organs. Most often it develops in patients with advanced renal disease and rarely in the absence of it (uremic and nonuremic calciphylaxis) (1). The patient presented had several risk factors for calciphylaxis: ESRD on HDF, female gender, Caucasian race, therapy with warfarin, and secondary hyperparathyroidism with elevated levels of serum calcium and phosphate. Our patient was on HDF for 5 years before the development of calciphylaxis, and the longer patients are on hemodialysis (HD), the higher the likelihood of calciphylaxis (7). Several authors have reported correlation with a higher prevalence of calciphylaxis in patients on warfarin therapy, as was our patient. She first noticed signs of calciphylaxis 1 to 2 months prior to the diagnosis and initiation of treatment. Due to a relatively low incidence and progressive clinical course of the disease, diagnosis is often delayed (1). Distal calciphylaxis (located distally to the knees) is considered prognostically better than proximal (1). The patient presented with necrotic ulcers on the shins and extensive subcutaneous plaques on the medial part of the left thigh. Thus, a combination of distal and proximal calciphylaxis was observed. Due to the presence of ulcerative lesions, the prognosis was even poorer, with a reported mortality rate as high as 80% (11).

Due to the high prevalence of generalized atherosclerosis in CKD patients (12), duplex ultrasound examination was performed in this patient, but it did not confirm peripheral artery disease. Ultrasonographic signs of superficial peripheral venous insufficiency were found; however, painful eschars on the lower extremities are not characteristic of venous ulcers. Several other diseases can mimic calciphylaxis clinically: vasculitis, superficial thrombophlebitis, purpura fulminans, warfarin necrosis, Martorell ischemic hypertensive ulcer, pyoderma gangrenosum, cholesterol embolization, oxalate vasculopathy, antiphospholipid syndrome, and nephrogenic systemic fibrosis (8, 13). Extensive laboratory evaluation and histopathological examination confirmed a definitive diagnosis of calciphylaxis. A biopsy is the gold standard diagnostic procedure in calciphylaxis. Nevertheless, according to a recent study, the majority of patients (57%) are diagnosed clinically (14).

The treatment of calciphylaxis is usually multidisciplinary, involving a nephrologist, dermatologist, wound care nurses, and other specialists (15). Measures of conventional treatment (7-9) were implemented in this patient: therapy with warfarin was discontinued, serum calcium, phosphorus, and parathyroid hormone levels were kept near normal values with cinacalcet and sevelamer, HDF sessions were prolonged, a dialysate with low calcium was used, and targeted systemic antibiotic treatment of cellulitis was administered. Analgesia is one of the most challenging aspects of calciphylaxis treatment because of the severity and complexity of the pain, which is thought to be ischemic in origin with a neuropathic component. Multimodal analgesia with high-dose opioids and benzodiazepines was used effectively in the patient (16). The aim of wound care is to control exudate, remove necrotic devitalized tissue, prevent infection, and improve wound healing. Surgical debridement has been used by some physicians (14, 17), whereas other researchers are more in favor of a conservative wound approach (19). Some alternative treatments for calciphylaxis have been described, such as therapy with bisphosphonates (18), low-dose tissue plasminogen activator infusions, LDL-apheresis, vitamin K, hyperbaric oxygen, kidney transplantation, and STS (8).

STS (also named sodium hyposulfite, chemically Na₂O₃S₂ or Na₃S₄O₆) is the most common drug being used off-label to treat calciphylaxis, primarily used for the treatment of cyanide poisoning and uremic calciphylaxis, and as nephroprotection during cisplatin administration. The mechanisms of STS action are not clear. STS induces calcium removal through chelation and prevents crystal formation and vascular calcification. It also exhibits antioxidative and vasodilation properties, which may contribute to a rapid resolution of the symptoms (19, 20).

Various modes of STS application in calciphylaxis have been reported: intravenous, intra-venous during HD sessions, oral, intra-peritoneal, intraleseional, and topical. The optimal dose, regimen, and duration of treatment have not yet been established (4, 5). Recent systematic reviews of treatment of uremic calciphylaxis with systemic STS have reported a significantly lower overall mortality rate of 38 to 50% (4, 21), compared to a 50 to 80% mortality rate after conventional treatment (8, 9). STS has several possible adverse effects, the most common ones reported being nausea, vomiting, and metabolic acidosis, followed by hypotension, headache, nephrotension, and bone demineralization (4, 22). With intra-dialytic application, a better patient survival rate and fewer problems with metabolic acidosis were reported compared to post-dialytic use (23). However, in a recent review, no significant difference in efficacy between intravenous, intra-dialysis, intra-peritoneal, and oral STS administration was found (4). Possible adverse events should be taken into consideration when deciding how to treat a fragile ESRD patient with calciphylaxis. In this patient we decided on intra-dialytic therapy with STS three times weekly, and no serious adverse effects were observed except for a few episodes of mild hypotension.

There is no consensus on the duration of treatment with intravenous STS. According to the literature, the therapy has reportedly been applied from 2 to 8 months (17, 24). The majority (80%) of patients have been treated with systemic STS for less than 3 months (14). In the patient presented, the treatment with STS was continued for 8 months due to the extensiveness of skin lesions and good tolerability of STS.

Intravenous STS has also shown promising results in the treatment of other types of CC; for example, dystrophic CC, which is the most common type of CC and can be associated with various autoimmune connective tissue diseases (25, 26).

Moreover, intravenous STS has also shown a positive effect on the delayed progression of coronary artery calcification in hemodialysis patients (26). During the treatment with STS in this patient, significant improvement in her physical and psychological condition was observed. Unfortunately, no objective examination to prove the observation was performed. The improvement might be due to a decrease in pain and inflammation; however, we can speculate that systemic treatment with STS might have also had positive effects on the patient’s cerebral atherosclerosis (27).

To avoid systemic exposure and adverse events, some authors have reported successful treatment of localized calciphylaxis with an intralesional application of STS (5, 8, 24, 28). Based on these reports, one intralesional treatment with STS was performed in the case presented. Due to large skin area involvement and the need for multiple repeated and relatively painful skin injections,
intralesional treatment with STS was discontinued. Moreover, repeated skin punctures pose an increased risk for skin infection, which is a serious complication in calciphylaxis. Several authors have also reported on effective treatment with topical preparations containing 10 to 25% STS for dystrophic, iatrogenic, and tu- moral CC (29, 30).

Conclusions

In the case presented of a patient with uremic calciphylaxis with extensive and ulcerated lesions on the lower extremities, compli-
cated by two episodes of cellulitis, the initial prognosis was poor and the treatment challenging. A multidisciplinary approach with an off-label intravenous STS treatment, careful wound manage-
ment, and other supportive measures resulted in successful healing of the skin lesions after 8 months and improvement of the patient’s general health condition. In spite of growing evidence of the efficacy of STS in the treatment of calciphylaxis, it is still considered an off-label therapy, thus hindering its more extensive use. Knowledge of advances in the treatment of calciphylaxis, which was previously a highly fatal disease, is important for phys-
icians and other professionals from various medical fields.

References

1. Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in prevention, diagno-
2. Nigwekar SU, Wolf M, Sterns RH, Hix JR. Calciphylaxis from nonuremic causes: a
rare but potentially fatal event of chronic kidney disease. Case report. An Bras
thiosulfate in treating calciphylaxis in chronic kidney disease patients. Nephrol-
ology (Carlton). 2018;23:669–75.
sodium thiosulfate for the treatment of calciphylaxis. JAMA Dermatol. 2013;149:
946–9.
6. Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-
1:38–41.
8. Nigwekar SU, Krosinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA,
2015;65:133–46.
10. Jiménez-Gallo D, Ossorio-García L, Linares-Barrios M. Calcinosis cutis and calci-
11. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome
12. Okamoto S, Iida O, Mano T. Current perspective on hemodialysis patients with
Isolated collagenoma on the face: a rare occurrence

Fouzia Siraj1 ✉, Sharma Shruti1, Geeti Khuller2, Ashok Saxena2

Abstract

Collagenomas are connective tissue nevi with hamartomatous proliferations of dominant dermal collagen. They can present as solitary or multiple inherited or acquired lesions over various body sites. The face is a rare site of collagenomas and, of the few cases reported in the literature, they have been seen more often on the scalp or on the plantar area. An extensive literature search did not reveal any cases of isolated collagenoma on the face. Herein we present the case of 22-year-old female with isolated collagenoma on the face. This case is being reported because of its unique location and rarity.

Keywords: collagenoma, isolated, nevi

Introduction

Connective tissue nevi are hamartomatous proliferations of the connective tissue components in the dermis. Uitto et al. classified them on the basis of their inheritance pattern and the involvement of the predominant extracutaneous connective tissue component: collagen, elastic fibers, or proteoglycans (1). Those with dominant dermal collagen are identified as collagenomas and have been specified as the Lipschutz type, whereas those with predominant elastic tissue changes are the Lewandowsky type (1). They can be solitary or multiple, and inherited or acquired. Collagenomas usually present as asymptomatic skin-colored plaques, papules, or nodules of various sizes in solitary, grouped, linear, or irregular distribution. Acquired collagenomas are called eruptive collagenomas when multiple, and when they are single or restricted to one body site they are called isolated collagenomas (2). Collagenomas usually occur over the upper trunk, arms, back, thighs, and soles (2). The face is a rare site of collagenomas and, among the few cases reported in the literature, they have been more often seen on the scalp or on the plantar area. To the best of our knowledge, only 18 reported cases of isolated collagenoma could be retrieved in English literature by searching on PubMed, out of which the majority of cases were on the scalp or on the plantar area. An extensive literature search did not reveal any cases of isolated collagenoma on the face. Herein we present the case of 22-year-old female with isolated collagenoma on the face. This case is being reported because of its unique location and rarity.

Case report

A 22-year-old female presented to the dermatology department with eruption of multiple, coalescing skin-colored to brown papules varying from 2 mm to 10 mm in size on the left side of the face that had appeared 6 months prior (Fig. 1). The lesions were asymptomatic but progressive. The history of injury and family history of similar skin lesions was negative. Systemic examination and routine hematological and biochemical investigations were within normal limits. Clinical differentials of connective tissue nevus, nevus sebaceous, and nevus lipomatosis superficialis were made. A punch biopsy was taken, which upon histopathological examination showed mildly acanthotic epidermis with mild nonspecific chronic perivascular inflammation in the upper dermis. Lobules of acellular, collagenized connective tissue in a haphazard arrangement were seen in the reticular dermis (Fig. 2), insinuating between the dermal appendages. The adnexal structures were preserved and no inflammatory cells were observed around them. Verhoeff–Van Gieson (VVG) stain for elastic fibers revealed marked reduction and fragmentation of elastic fibers (Fig. 3), thereby confirming that the connective tissue lobules consisted of collagen. Based on these findings, the patient was diagnosed as having isolated collagenoma. No specific treatment was given because the patient was lost to follow-up.

Discussion

Collagenomas are now usually classified into four groups, two inherited and two acquired. The inherited ones are 1) familial cutaneous collagenomas and 2) shagreen patches of tuberous sclerosis, and the acquired ones are 3) eruptive collagenomas and 4) isolated collagenomas. Familial cutaneous collagenomas have an autosomal dominant inheritance, are present in a symmetrical distribution on the upper trunk, and are associated with extracutaneous abnormalities such as sensorineural hearing loss, recurrent vasculitis, and cardiac disorders such as idiopathic cardiomyopathy.

Figure 1 | Multiple skin-colored papules varying from 2 mm to 10 mm in size on the left side of face.

1National Institute of Pathology (ICMR), Safdarjung Hospital Campus, New Delhi, India. 2National Institute of Dermatology (VMMC), Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India. ✉Corresponding author: fouziasiraj2009@gmail.com

Received: 2 July 2018 | Returned for modification: 4 September 2018 | Accepted: 4 October 2018
Table 1 | Eighteen cases of isolated collagenoma.

<table>
<thead>
<tr>
<th>No.</th>
<th>Country</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Family history</th>
<th>Site</th>
<th>Histopathology</th>
<th>Treatment</th>
<th>Workup</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Taiwan</td>
<td>8</td>
<td>M</td>
<td>−</td>
<td>Left upper arm</td>
<td>Papulolinear collagenoma</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Brazil</td>
<td>3</td>
<td>F</td>
<td>−</td>
<td>Lower back</td>
<td>Papulolinear collagenoma</td>
<td>Not mentioned</td>
<td>MRI, CT scan</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Brazil</td>
<td>45</td>
<td>F</td>
<td>−</td>
<td>Hands, fingers</td>
<td>Papulolinear collagenoma</td>
<td>Not mentioned</td>
<td>Skeletal survey</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Turkey</td>
<td>26</td>
<td>F</td>
<td>−</td>
<td>Proximal part of left arm</td>
<td>Eruptive collagenoma</td>
<td>Refused treatment</td>
<td>Not mentioned</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Iran</td>
<td>14</td>
<td>M</td>
<td>−</td>
<td>Frontal</td>
<td>Isolated collagenoma</td>
<td>Intralesional triamcinolone acetonide injections</td>
<td>MRI, CT scan</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>India</td>
<td>23</td>
<td>F</td>
<td>−</td>
<td>Labium majus</td>
<td>Isolated collagenoma</td>
<td>Refused treatment</td>
<td>Not mentioned</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>India</td>
<td>20</td>
<td>M</td>
<td>−</td>
<td>Scalp</td>
<td>Isolated collagenoma</td>
<td>Surgery</td>
<td>MRI, CT scan</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>India</td>
<td>18</td>
<td>F</td>
<td>−</td>
<td>Lower back</td>
<td>Isolated corymbose collagenoma</td>
<td>Intralesional triamcinolone hyaluronidase</td>
<td>MRI, CT scan</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>India</td>
<td>20</td>
<td>M</td>
<td>−</td>
<td>Scalp</td>
<td>Isolated pedunculated collagenoma Isolated cerebriform collagenoma</td>
<td>Surgical excision</td>
<td>MRI, CT scan</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>India</td>
<td>9</td>
<td>F</td>
<td>−</td>
<td>Plantar of right foot</td>
<td>Isolated collagenoma</td>
<td>Not mentioned</td>
<td>Skeletal survey</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>Japan</td>
<td>6</td>
<td>F</td>
<td>−</td>
<td>Scalp</td>
<td>Isolated collagenoma</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>United States</td>
<td>40</td>
<td>F</td>
<td>−</td>
<td>Toe, plantar of right foot</td>
<td>Isolated collagenoma</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>India</td>
<td>35</td>
<td>F</td>
<td>−</td>
<td>Scalp</td>
<td>Isolated collagenoma</td>
<td>Not mentioned</td>
<td>Skeletal survey</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>Turkey</td>
<td>19</td>
<td>F</td>
<td>−</td>
<td>Plantar right foot</td>
<td>Isolated collagenoma</td>
<td>Surgical excision</td>
<td>ECG, echo skeletal survey</td>
<td>16</td>
</tr>
<tr>
<td>15</td>
<td>Korea</td>
<td>23</td>
<td>F</td>
<td>−</td>
<td>Toe, plantar of right foot</td>
<td>Isolated collagenoma</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>17</td>
</tr>
<tr>
<td>16</td>
<td>India</td>
<td>22</td>
<td>M</td>
<td>−</td>
<td>Palm</td>
<td>Isolated collagenoma</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>18</td>
</tr>
<tr>
<td>17</td>
<td>Switzerland</td>
<td>11</td>
<td>M</td>
<td>−</td>
<td>Plantar of right foot</td>
<td>Isolated collagenoma</td>
<td>Surgeon refused excision</td>
<td>Skeletal survey</td>
<td>19</td>
</tr>
<tr>
<td>18</td>
<td>Spain</td>
<td>6</td>
<td>F</td>
<td>−</td>
<td>Toe, plantar of right foot</td>
<td>Isolated collagenoma</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>20</td>
</tr>
<tr>
<td>19</td>
<td>India</td>
<td>22</td>
<td>F</td>
<td>−</td>
<td>Face</td>
<td>Isolated collagenoma</td>
<td>No follow-up</td>
<td>–</td>
<td>Present case</td>
</tr>
</tbody>
</table>

F = female, M = male, MRI = magnetic resonance imaging, CT = computed tomography.
and congestive heart failure. Shagreen patches of tuberous sclerosis also have a family history and are associated with other characteristic cutaneous manifestations of adenoma sebaceum, subungual fibroma, and ash leaf macules (2). Both eruptive and isolated collagenomas are acquired connective tissue nevi of the collagen type and lack a family history. Although the histopathological features of both are the same, isolated collagenomas are localized to a single body region, as in our case. Varying presentations of isolated collagenomas such as paving stone nevi, plantar fibromatosis, and papulonodular and zosteriform lesions have been reported in the literature (3, 4). The pathogenesis of collagenomas or connective tissue nevi is unclear and, because they are benign, no specific treatment is currently given in most cases (2). According to Uitto et al., collagenomas are composed exclusively of type I collagen. They form due to reduced production of collagenase, causing reduced degradation of collagen locally (5). Histopathological examination is the gold standard for diagnosis. In diagnosed cases, a further workup is necessary to rule out any underlying systemic disorder because collagenomas have been associated with disorders such as hypogonadism, pseudohypoparathyroidism, and Down syndrome (2). Diagnosis of isolated collagenoma was made by a combination of standards, including lack of family history and extracutaneous manifestations, single location, and classical clinical and histopathological features.

We are reporting this case because of its unique location, rarity, and absence of any associated abnormalities. Publication of such cases should be encouraged because this may be an underdiagnosed entity and awareness of it would improve the recognition of this condition.

References

ČISTO*

* Po enem letu zdravljenja je imelo 52 % bolnikov PASI 100.¹

VIDNI REZULTATI V 2. TEDNU**

** Zdravilo Taltz je bilo povezano s hitrim nastopom učinkovitosti z > 50 % znižanjem povprečne ocene PASI do 2. tedna.²
Atrophoderma of Pasini and Pierini in a young adult: a case report

Antigona Begolli Gerqari\textsuperscript{1} \textsuperscript{✉}, Mybera Ferizi\textsuperscript{1}, Idriz Gerqari\textsuperscript{2}

\textsuperscript{1}Dermatovenerology Clinic, University Clinical Center, Prishtina, Kosovo. \textsuperscript{2}Nuclear Medicine Department, University Clinical Center, Prishtina, Kosovo.

\textsuperscript{✉}Corresponding author: antigonagerqari@gmail.com

Introduction

Atrophoderma of Pasini and Pierini is a skin disease manifested with depressed skin in areas that have a histopathology confirmed as atrophy with hyperpigmentation. The disease was first described by Pasini in 1923 and subsequently by Pierini in 1936. They distinguished this form of atrophy from other diseases and conditions in which the atrophy is morphologically and clinically different. The disease was initially associated with \textit{Borrelia burgdorferi} infection; however, at present, various theories have emerged for the appearance of the disease, linked to genetic, neurogenetic, and immunological factors. Here we present a patient that was admitted to the hospital due to disseminated lesions on the skin of the lower limbs, with slightly pigmented and atrophic skin along with irregular borders varying in size, from several mm to a few cm, clearly demarcated from the healthy skin, with no history of a tick bite or a family history of similar skin disorders.

Case report

Here we report a case study of a 20-year-old man attending our outpatient clinic with a 2-year history of slightly depressed hyperpigmented patches of the skin of the lower limbs. The patient had noticed that the changes were more visible during autumn and winter, whereas in summer the skin patches become less intense in color. The patient was initially treated as an outpatient with local corticosteroids, and nourishing and neutral creams. The patient was subsequently admitted, presenting with disseminated lesions on the skin of the lower limbs (Fig. 1), with slightly pigmented and atrophic skin along with irregular borders. The skin lesions varied in size from a few mm to several cm and were clearly demarcated from the surrounding healthy skin. After admission to the hospital, we carried out the following analyses: sedimentation, full blood count, urea, creatinine, hepatogram, transaminases, anti-DNA, antinuclear antibody (ANA), LE cell, Scl-70, CRP, and serological test for \textit{Borrelia}. All parameters were within reference ranges. The only collateral finding that we noticed was subclinical Hashimoto’s thyroiditis with a normal level of thyroid hormones and very high levels of anti-TPO (1,200 in a reference range of < 30 IU/ml). The previously unidentified thyroiditis was detected by a dermatologist during the hospitalization at our clinic because the patient did not have any noticeable symptoms before admission. Moreover, a detailed skin biopsy report, obtained via standard pathology diagnostics services, revealed flattening of the dermal papillae rete ridges, perivascular, peril follicular lymphocytic infiltrate, and clumping of collagen fibers.

Abstract

Atrophoderma of Pasini and Pierini is a skin atrophy presenting as single or multiple sharply demarcated, hyperpigmented, non-indurated patches, with a slight depression of the skin, that can converge and form a confluent area with atrophy as a consequence. The condition was first described by Pasini in 1923 and subsequently by Pierini in 1936. They distinguished this form of atrophy from other diseases and conditions in which the atrophy is morphologically and clinically different. The disease was initially associated with \textit{Borrelia burgdorferi} infection; however, at present, various theories have emerged for the appearance of the disease, linked to genetic, neurogenetic, and immunological factors. Here we present a patient that was admitted to the hospital due to disseminated lesions on the skin of the lower limbs, with slightly pigmented and atrophic skin along with irregular borders varying in size, from several mm to a few cm, clearly demarcated from the healthy skin, with no history of a tick bite or a family history of similar skin disorders.

Keywords: atrophoderma of Pasini and Pierini, atrophy, hyperpigmentation

Received: 28 June 2018 | Returned for modification: 24 October 2018 | Accepted: 29 November 2018
Case analysis including histological findings suggested that the patient was suffering from atrophoderma of Pasini and Pierini. The patient was discharged from the hospital with advice to apply cream containing topical steroids, having rejected our suggestions for therapy with hydroxychloroquine or retinoids. During routine follow-up and regular controls we did not notice any improvement of the patient’s condition.

Discussion

Atrophoderma of Pasini and Pierini is a disease with an unknown cause (2, 4), even though in some cases Borrelia burgdorferi was the primary factor as a cause due to findings of high Borrelia antibody titers in some patients with atrophoderma of Pasini and Pierini (10). In this particular case, serological tests for Borrelia were negative. Nevertheless, the role of Borrelia burgdorferi infection in the pathogenesis of atrophoderma of Pasini and Pierini remains disputable. Some studies suggest that a neurogenic cause, immunological factors, and genetic predisposition may play significant roles in the appearance of the disease (11, 12). A connection with morphea was also determined due to the similarity of our findings in the skin (13) because we found no evidence of an inflammatory process. The classification of atrophoderma is a challenge in medical literature, and differential diagnostics should include other disorders identified by skin atrophy. Some authors have classified atrophoderma as a disease with a long course and a unique appearance without signs that resemble morphea, including characteristic lilac rings (13), which were observed in the case presented. The disease is characterized by a single or sometimes multiple confluent depressed hyperpigment-ed atrophic scars appearing in patches, with a distinctive border known as the “cliff-drop” border. The typical area affected is the back, but other regions can be affected and there is significant symmetry. In our case, symmetry was evident but the location of the disease was unusual because the changes were concentrated on the lower extremities and numbered more than 50. The disease mostly appears in early adolescence and it affects females more than males (5–9). These cases describe the disease in children and elderly female patients, whereas here we present a case of atrophoderma of Pasini and Pierini in an adult male. Laboratory evaluations were within normal range and histological examination revealed a characteristic decrease of dermal thickness. The course of the disease is usually benign, but the poor response to conventional therapy is considered a problem for both the patient and the physician (10, 14). Skin changes that persist and remain the same size over time nonetheless sometimes develop further and increase in both number and size for 10 to 20 years without a significant improvement despite treatment.

The diagnosis is based on clinical findings and skin biopsy (13). However, treatment does not show significant results. Some positive results have been achieved with retinoids and topical steroids. In some cases there have also been good reports on administration of hydroxychloroquine (14). In cases in which Borrelia burgdorferi infection is documented, a course of antibiotics with oral doxycycline. Ann Dermatol. 2011;23:352–6.

References

Unusual photodermatosis with lichenoid eruption and apoptosis in a 33-year-old female

Jordan M. Montoya1 ✉, David J. DiCaudo1, Aaron R. Mangold1, David L. Swanson1

1Mayo Clinic School of Medicine, Scottsdale, AZ, United States. ✉ Corresponding author: Montoya.Jordan@mayo.edu

Abstract

We describe the clinical and dermoscopic features and histopathological findings in a case of a 33-year-old female patient with an adult-onset photodermatosis. This eruption was not typical of well-established photodermatoses due to its apoptotic keratinocytes. To our knowledge, this is the first report of these combined clinical and pathologic features.

Keywords: photodermatoses, hydroa, lichenoid eruption, photosensitive disorders

Introduction

Photodermatoses are rashes that develop after sun exposure. Idiopathic photodermatoses unrelated to secondary causes are loosely classified into the following categories: polymorphic light eruption (PMLE), actinic prurigo, hydroa vacciniforme (HV), chronic actinic dermatitis, and solar urticaria. The exact pathomechanism of many of these skin reactions remains unknown. Clinical recognition of the lesions along with phototesting and histopathological findings are essential in establishing the diagnosis among idiopathic photodermatoses. Herein we describe a case and dermoscopic findings of an unusual photodermatosis with lichenoid pathology and necrotic keratinocytes that was diagnosed by clinical features, dermoscopic findings, and histopathological findings.

Case report

A 33-year-old Native American woman presented with a seasonal rash on her arms that first appeared in her late teens. The rash began in the summertime and erupted several hours after sun exposure. The rash presented as small pruritic erythematous papules on her face, ears, and arms; the trunk and lower extremities were spared. The rash completely resolved in the winter with no evidence of scarring. Serological tests for lupus and rheumatoid arthritis were negative. She achieved partial relief with triamcinolone and diphenhydramine.

Physical examination showed numerous monomorphic, pink papules on the dorsal forearms (Fig. 1) without scaling, erosion, or blistering. The upper arms and dorsal hands were unaffected, as were the back, lower extremities, and ears. When examined with contact polarized dermoscopy, the papules were white and poorly marginated (Fig. 2). Contact non-polarized dermoscopy showed poorly marginated papules, some of which showed course granularity and white scale (Fig. 3). There was no evidence of scarring.

A punch biopsy specimen from the forearm showed intra-epidermal vesicles with focal epidermal necrosis and mild to moderate perivascular lymphocytic dermal inflammatory infiltrate. (Fig 4). There were numerous necrotic keratinocytes with overlying parakeratosis present in the epidermis. The lymphocytic inflammatory infiltrate consisted mostly of CD3-positive T-cells, with smaller populations of CD4+ and CD8-positive cells. The CD56 immunostain and in situ hybridization for Epstein–Barr virus were negative.

The patient was prescribed triamcinolone for active flares. She was encouraged to use oral Polypodium leucotomos, zinc/titanium-based sunscreens, and barrier clothing sun protection for prevention.

Figure 1 | Numerous monomorphic, pink papules on the dorsal forearm.
Discussion

This case defied a unifying diagnosis from clinical and histopathology findings. Hydroa aestivale (HA) was initially felt to be the most likely diagnosis. HA clinically presents with papules, macules, and vesicles that appear 1 to 2 hours after exposure to sunlight, ultraviolet light, or visible light. The rash is limited to sun-exposed skin, and most intensely occurs on the ears, neck, and arms. It is characterized by erythema of the exposed field, accompanied by macules, papules, and vesicles. The vesicles are typically associated with a burning sensation or pruritus. HA usually does not scar and is familial in up to 10% of cases. It most frequently presents in childhood, and it resolves by the onset of puberty or the late teens (2, 3). This is inconsistent with our case, in which the photodermatoses presented after the onset of puberty. The histopathology is consistent with HA. However, the lack of reports on HA as a confirmed, separate diagnosis from HV and the inconsistent clinical picture suggest that this is not HA.

The differential diagnosis of HA includes other photosensitive disorders that present with lesions on the skin after visible light exposure, such as HV, pinpoint PMLE, lichen nitidus, and actinic prurigo. HV was ruled out on clinical morphological differences and the absence of crusts and varioliform scarring after sun exposure that are typically seen with and without dermoscopy (5). It is controversial whether HA is a distinct entity from HV (4). Lichen nitidus presents with pink macules as seen in our case; however, the dermoscopic appearance is one of elevated, shiny macules with radial ridges, and a surrounding reddish vascular network (6). The histopathology of lichen nitidus is distinctive, and it differs markedly from this case (7). PMLE heals without scarring but lacks necrotic keratinocytes (8). Actinic prurigo manifests as a photodermatosis of sun-exposed areas of the skin, but its histopathologic characteristics are nonspecific and do not include necrotic keratinocytes (9). There are no reports at this time of the dermoscopic features of HA, HV, PMLE, and actinic prurigo.

In summary, we present a case and dermoscopic findings for a 33-year-old woman whose clinical and histopathologic features were not consistent with HA, HV, lichen nitidus, PMLE, and actinic prurigo. We are soliciting similar case presentations.

References

Retraction note: Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report

We, the editors of the journal *Acta Dermatovenerologica Alpina, Pannonica et Adriatica* (Acta Dermatovenerol APA), would like to retract the article “Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report” (PMID: 29589642; DOI: 10.15570/actaapa.2018.6) published in our journal’s March 2018 issue due to duplicate publication.

We were informed in February 2019 by a third party that an article very closely resembling the article “Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report” published by Yesim Akpinar Kara and Evren Sarifakioglu in Acta Dermatovenerol APA in 2018 (1) had been published by the same authors under the exactly the same title in *Journal of the Turkish Academy of Dermatology* (J Turk Acad Dermatol) in late 2017 (DOI: 10.6003/jtad.17113c1) (2).

Following our initial concern, submission history of the article in question was carefully reviewed. The manuscript (originally titled “A rare case of atrophoderma with papules”) was submitted to Acta Dermatovenerol APA on July 1st, 2017. As a part of our regular editorial procedure, which includes inspection of all newly submitted manuscripts for plagiarism using plagiarism software, the manuscript was checked for plagiarism and was found to have a very low (2%) identity score index with previously published research. Following peer-review, the manuscript was returned to the authors for revision (revision letter sent on July 24th, 2017). The manuscript was finally accepted for publication in Acta Dermatovenerol APA on August 27th, 2017; an acceptance letter was sent to the corresponding author on the same day. The manuscript was then copyedited by a native English speaker and was published in the March 2018 issue of Acta Dermatovenerol APA (publication date March 31st, 2018).

Although the identity score index of the initially submitted manuscript was very low when checked in July 2017, further comparison performed in February 2019 of the initial manuscript text submitted to Acta Dermatovenerol APA (i.e., before the English proofreading) with the article published in J Turk Acad Dermatol showed that both articles were virtually identical. Our editorial office immediately contacted Akpinar Kara regarding our findings, requesting a detailed explanation of how duplicate publication had occurred. In her reply, Akpinar Kara stated that the manuscript had indeed also been sent to J Turk Acad Dermatol (no exact date of submission provided), but that no reply from J Turk Acad Dermatol was received for a significant period of time. Moreover, Akpinar Kara claimed that the authors had not received any feedback from J Turk Acad Dermatol, including a peer review, and were only notified via e-mail 1 year after submission that the article had been accepted for publication in J Turk Acad Dermatol.

The editor-in-chief of J Turk Acad Dermatol was contacted and provided with the statements by Akpinar Kara. Contrary to the claims of Akpinar Kara, the editorial office of J Turk Acad Dermatol claimed that the manuscript was added to their editorial system by Akpinar Kara on October 8th, 2017 (i.e., 3 months after submission to Acta Dermatovenerol APA and more than a month after the authors were informed that their manuscript had been accepted for publication in Acta Dermatovenerol APA). Moreover, contrary to the claims by Akpinar Kara, J Turk Acad Dermatol informed us that the manuscript had been subjected to peer-review (two independent reviews) and that an acceptance letter was sent to Akpinar Kara on January 23rd, 2018 via e-mail. Finally, J Turk Acad Dermatol informed us that a revised version of the manuscript was submitted to J Turk Acad Dermatol by the author via their editorial system on January 29th, 2018.

Based on all the information provided above, we are retracting the article “Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report” (PubMed PMID: 29589642; DOI: http://dx.doi.org/10.15570/actaapa.2018.6) published in the March 2018 issue of Acta Dermatovenerol APA due to duplicate publication.

References


Lokalno zdravljenje aktiničnih keratoz

Učinkovito zdravljenje in zelo dober kozmetični izid po 2 ciklih zdravljenja

- odkriva subklinične aktinične keratoze v obeh ciklih zdravljenja
- učinkovito in dolgotrajno odstrani subklinične in klinične lezije ne glede na njihovo število
- režim zdravljenja določa premor med dvema cikloma za omilitev kožne reakcije

Zyclara 3,75 % krema

Sestava: Ena vrečica vsebuje 9,375 mg imikvimoda v 250 mg kreme (3,75 %). En gram kreme vsebuje 37,5 mg imikvimoda.

Zdravilo Zyclara (za en nanos: do 2 vrečici, 250 mg imikvimod kreme na vrečico) nanašamo enkrat na dan pred spanjem na kožo prizadetega predela.

Neželeni učinki:

- eritem, krasta, luščenje kože, kožni edem, kožne razjede, hipopigmentacija kože, eritem na mestu aplikacije, nastajanje
- vlaženja in razvijanje aktiničnih keratoz (AK) na celotnem obrazu ali na neporaščenem izhodišču.

Imetnik dovoljenja za promet z zdravilom: Meda AB, Pipers väg 2, 170 73 Solna, Švedska.

Indikacije:

- pri kožnih navadi, ki so atipične za AK
- pri sumu na malignost
- pri lezijah, ki so osebno odlične za AK

Preševanje: Podatkov ni na voljo.

1. cikel
- 1. teden
- 2. teden
- 6. teden
- 14. teden

2. cikel
- 3. teden
- 4. teden
- 2. cikel

Ostali neželeni učinki so navedeni v Povzetku glavnih značilnosti zdravila. Način in režim izdaje zdravila: Ena vrečica vsebuje 9,375 mg imikvimoda v 250 mg kreme (3,75 %). En gram kreme vsebuje 37,5 mg imikvimoda.


o odkriva subklinične aktinične keratoze v obeh ciklih zdravljenja
- učinkovito in dolgotrajno odstrani subklinične in klinične lezije ne glede na njihovo število
- režim zdravljenja določa premor med dvema cikloma za omilitev kožne reakcije

Varnost in učinkovitost imikvimoda pri aktinični keratozi pri otrokih

Medsebojne interakcije

- Pogost: herpes simpleks, limfadenopatija, anoreksija, zvrsna videnost glukoze v krvi, nespečnost, glavoč, omočica, navzea, danar, buhanje, dermatitis, mialgia, artralgie, reakcija na mestu aplikacije, prihujenje na mestu aplikacije, bolečine, bolečine v prsih.

Varnost in učinkovitost imikvimoda pri aktinični keratozi pri ovdovitih in mladinskih

Medsebojne interakcije

- Pogost: herpes simpleks, limfadenopatija, anoreksija, videnost glukoze v krvi, nespečnost, glavoč, omočica, navzea, danar, buhanje, dermatitis, mialgia, artralgie, reakcija na mestu aplikacije, prihujenje na mestu aplikacije, bolečine, bolečine v prsih.

Posamezni ciklus zaradi pozabljenih odmerkov ali obdobij prekinitve ne sme biti daljši od 2 tednov.

Zdravilo se enkrat na dan pred spanjem nanese na kožo prizadetega predela, kjer naj ostane 8 ur. V tem času se je treba izogibati prhanju ali kopanju. Pred vsakim nanašanjem kreme in po njem si je treba dobro umiti roke.

Če bolnik pozabi uporabiti odmerke, naj počaka do naslednjega večera in zdravilo Zyclara uporabi takrat, nato pa naj nadaljuje z običajnim umikom zdravljenja. Kreme se ne sme nanesti na kožo več kot enkrat na dan.

Posamezni ciklus zaradi pozabljenih odmerkov ali obdobij prekinitve ne sme biti daljši od 2 tednov.

Samo za strokovno javnost!
Editorial expression of concern: The measurement of serum TNF-α levels in patients with lichen planus

After the duplicate publication of an article by Yesim Akpinar Kara was identified (1–3), concerns were raised whether other cases of scientific misconduct occurred by the same author. The editorial office of Acta Dermatovenerologica Alpina, Pannonica et Adriatica (Acta Dermatovenerol APA) searched for and reviewed all manuscripts submitted to our journal by Akpinar Kara. In addition to the first case of duplicate publication described in detail in this issue of Acta Dermatovenerol APA (1), we identified another case of duplicate publication by the same author: the article “The measurement of serum tumor necrosis factor-alpha levels in patients with lichen planus” by Y. Akpinar Kara published in the July/August 2018 issue of Indian Journal of Dermatology (Indian J Dermatol) (PMID: 30078872; DOI: 10.4103/ijd.IJD_474_17) (4) was practically identical to the original article “The measurement of serum TNF-α levels in patients with lichen planus” published in the December 2017 issue of Acta Dermatovenerol APA (PMID: 29264897; DOI: 10.15570/actaapa.2017.26) (5) by the same author. In February 2019, the editorial office of Acta Dermatovenerol APA contacted both the author as well as the editors of Indian J Dermatol. Pending the final resolution of this case, Acta Dermatovenerol APA is publishing this editorial expression of concern.

References

15 ODOBRENIH INDIKACIJ

Več kot 1.100.000 BOLNIKOV po svetu se zdari z zdravilom HUMIRA

74 KLINIČNI RAZISKI

v največji publikaciji o varnosti zaviralcev TNF-α

Že 14. LETO v Sloveniji

20 LET KLINIČNIH IZKUŠENJ

z začetki pri revmatoidnem artritisu

HUMIRA

Edinstveni temelji za prihodnost

Švedski Štartov, za 14. Leto HUMIRA v Sloveniji

1.100.000 BOLNIKOV po svetu se zdari z zdravilom HUMIRA

20 LET KLINIČNIH IZKUŠENJ

z začetki pri revmatoidnem artritisu

HUMIRA

Edinstveni temelji za prihodnost

Švedski Štartov, za 14. Leto HUMIRA v Sloveniji

1.100.000 BOLNIKOV po svetu se zdari z zdravilom HUMIRA

20 LET KLINIČNIH IZKUŠENJ

z začetki pri revmatoidnem artritisu

HUMIRA

Edinstveni temelji za prihodnost

Švedski Štartov, za 14. Leto HUMIRA v Sloveniji

1.100.000 BOLNIKOV po svetu se zdari z zdravilom HUMIRA
Zdravilo 1. izbora za zdravljenje blagih do zmernih oblik akne

Po priporočilu NOVIH evropskih smernic za zdravljenje akne

Zdravilo BELAKNE:

1. za zdravljenje blagih do zmernih oblik akne
2. ima hiter učinek, bolniki ga dobro prenašajo (izboljšana komplianca)
3. preprečuje težje oblike bolezni
4. preprečuje nastanek brazgotin
5. zmanjšuje potrebo po dolgotrajni sistemski terapiji
6. priporoča se za vzdrževalno zdravljenje

Sestava: 1 mg/g gel ali 1 mg/g krema

Indikacije: Zdravljenje blagih do zmernih oblik akne s pretežno prisotnimi ogrančenji, papulami in pustulami na obrazu, prsih ali hrbtu.


Kontraindikacije: Preobčutljivost za zdravilno učinkovino ali katero koli pomožno snov; nosečnost; ženske, ki načrtujejo nosečnost.

Posebna opozorila in previdnostni ukrepi: Če se pojavi preobčutljivostna reakcija ali hudo draženje, je treba uporabo zdravila prekiniti.

Interakcije: Ni znanih interakcij pri sočasni uporabi zdravila Belakne z drugimi zdravili, ki jih lahko uporabljamo perkutano. Kljub temu pa zdravila Belakne lahko uporabljamo z druge sredstve za akni, ki lahko uporabljamo perkutano. Če želimo uporabiti zdravila Belakne s drugimi zdravili, ki lahko uporabljamo perkutano, je treba uporabiti zdravila Belakne skupaj s sistemskimi sredstvi ali izmed drugih zdravil.

Nova generacija Er:YAG in Nd:YAG laserskih sistemov v medicini

SP Dynamis

choose perfection

SP Dynamis

The Highest Performance, Best Made Laser Systems in the World

• Odstranjevanje benignih in pigmentnih sprememb na koži
• Zdravljenje aken
• Ablativno in neablativno pomlajevanje kože
• Izboljšanje videza brazgotin in strij
• Zdravljenje žil in drugih vaskularnih lezij
• Eplacija
• Neinvazivni posegi: TightSculpting®, Fotona 4D®, SmoothEye™
• Zdravljenje glivic in bradavic
• Zdravljenje smrčanja
• Kirurški posegi

Pot do popolnih rezultatov je enostavnejša z uporabo namenskih skenerjev in frakcionalnih ročnikov. SP Dynamis laserski sistem je vrhunski izdelek za vašo ordinacijo.
Poglejte na www.fotona.com še danes.
Sorel combo 50 mikrogramov/500 mikrogramov v 1 g mazilo v tubi s 60 g mazila

Za lokalno zdravljenje stabilne psoriaze vulgaris v plakih pri odraslih.

Sorel combo mazilo vsebuje kombinacijo kalcipotriola in betametazona.

SKRAŠANI POVZETEK GLAVNYH ZNAČILNOSTI ZDRAVILA

Sorel combo 50 mikrogramov/500 mikrogramov v 1 g mazilo

SESTAVA: En gram mazila vsebuje 50 mikrogramov kalcipotriola (v obliki monohidrata) in 0,5 mg betametazona (v obliki dipropionata). Za celoten seznam pomožnih snovi glejte poglavje 6.1 SmPCja.

TERAPEVTSKE INDIKACIJE: Topikalno zdravljenje stabilne psoriaze vulgaris v plakih pri odraslih, kjer je mogoče topikalno zdravljenje.


NEŽELJNI UČINKI: Pogosti: pruritis in luščenje kože. Občasni: bakterijske, glivične in virusne okužbe kože, atrifoli, keratodermija, atrofi kože, poslabšanje psoriaze, dermatitis, eritem, izpuščaj (eksfoliativni, papularni in pustularni), purpura ali ekhimose, proklinacije, škrotalno občutek na koži, draženje kože, izpuščanje pigmentacije na mestu nanosa, bolečina na mestu nanosa. Drugi manj pogosti neželjeni učinki so navedeni v SmPC.

MOČ JE V ZAŠČITI


Spremenite zaščito v preventivo.

Pred uporabo pazljivo preberite navodila. Za informacije o indikacijah, varnostnih ukrepih in stranskih učinkih se posvetujte z zdravnikom ali farmaceutom.

Pri odraslih bolnikih z zmerno do hudo psoriazo v plakih zagotavlja biološko zdravilo CIMZIA® kontinuiteto zdravljenja, ki ga potrebujejo skozi vse življenje.

SI-CIM-0219-002 Samo za strokovno javnost

Skrajšani povzetek glavnih značilnosti zdravila CIMzia/certolizumab pegol

Ime zdravila: Certolizumab pegol je fragment Fab'-rekončitvenega, humaniziranega protitela proti tumorje nekrotizirajočem faktorju alfa (TNF (PEG)).

Zdravljenje:

- Psoriaza v plakih: Po začetnem odmerku je vzdrževalni odmerek 200 mg vsaka 2 tedna za odrasle. Odmerjanje:
- Psoriatični artritis: Začetni odmerek zdravila Cimzia za odrasle bolnike je 400 mg (apliciran kot dve subkutani injekciji po 200 mg) na začetku zdravljenja, po 2 in 4 tednih. Po potrebi bolnik med zdravljenjem z zdravilom Cimzia še naprej prejema MTX. Vzdrževalni odmerek: Začetni odmerki je priporočeno vzdrževalni odmerek zdravila CIMzia pri odraslih bolnikih s psoriatičnim artritisom 200 mg vsaka 4 tedna. Po potrebi bolnik med zdravljenjem z zdravilom Cimzia še naprej prejema MTX. Ali prijevač: Po začetnim odmerki se priporoča vzdrževalni odmerek zdravila Cimzia pri odraslih bolnikih s psoriatičnim artritisom med zdravljenjem z zdravilom Cimzia še naprej prejema MTX. Vzdrževalni odmerek: Rekomendacije.

- Rezervnin: Osebe z zdravilom Cimzia pa priprave informacije.

- Datum priprave informacije: 02/2019.
IN ATOPIC DERMATITIS,
LOOKS CAN BE DECEIVING

- Current evidence suggests that nonlesional, or normal-looking, atopic skin is not normal because of persistent subclinical inflammation.
- Atopic dermatitis is a chronic immunologic skin disease in which IL-4 and IL-13 are key Th2 cytokines involved in the underlying inflammatory process.
- This subclinical inflammation throughout the body is a source of lesions and itch, primary signs and symptoms of atopic dermatitis.

DISCOVER THE INFLAMMATION BENEATH