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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

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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

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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).

Methods

We performed a prospective, randomized, and controlled split-face study in which the unit of randomization was the individual facial side of each patient.

Subjects were selected from the Department of Dermatology at Vila Nova de Gaia and Espinho Central Hospital from September to December 2015. Inclusion criteria were patients with a diagnosis of erythematotelangiectatic rosacea, older than 18, and with no other relevant comorbidities. All patients were naive to laser treatment or had had their last laser treatment more than 1 year prior. Exclusion criteria were the presence of inflammatory papules, pustules, or vesicles and facial telangiectasias greater than 2 mm in diameter. None of the patients had a history of photosensitivity, nor were any treated with a known photosensitizing medication in the prior month. Twenty-nine patients were initially included and 27 patients completed our study. Only patients that completed the study were included in the statistical analysis.

All subjects provided written informed consent. All the procedures described in this study were in accordance with national and institutional ethical standards and were approved in advance by local ethical review committees.

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

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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.

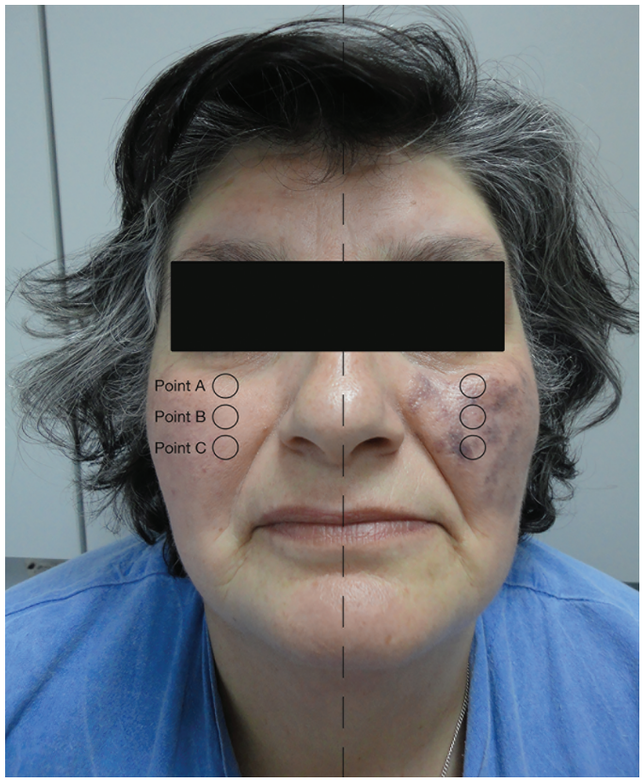

Figure 1 | Spectrophotometry measurement points and result immediately after treatment (left side treated with multiplexed PDL/Nd:YAG and right side with PDL).

Statistical analysis

Statistical analysis was conducted in SPSS version 24.0 (SPSS Inc., USA). Descriptive statistics and a *t*-test (unpaired and paired, two-tailed) were used when appropriate. Repeated-measures analysis of variance (ANOVA) were conducted to compare means at the data collection points. The results were considered statistically significant at $p < 0.05$.

Results

Twenty-nine patients were initially enrolled in the study. Two female patients dropped out after the first treatment because of unacceptable purpura that interfered with work and excessive pain during the treatment, respectively. The remaining 27 patients completed all three treatment sessions and a follow-up visit. Of these, 63.0% were females (17 out of 27 cases) and 37.0% were males (10 out of 27 cases). The mean age was 52.9 ± 15.9 years and no differences were observed between sexes (57.8 ± 17.0 years in males vs. 50.0 ± 14.9 years in females; $p = 0.224$). The proportion of patients older than 30 was 88.9% (24 out of 27 cases).

The DLQI, photograph evaluation, spectrophotometer meas-

urements, 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 6.15 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 photograph 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 (3.41 ± 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 (56.15 ± 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), spectro-

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

	Baseline	First treatment	Second treatment	Third treatment	*p* value
Cases (*n*)	29	27	27	27	
DLQI (mean ± *SD*)	6.15 ± 4.9	3.30 ± 3.5	1.74 ± 1.6	1.22 ± 1.2	0.001
Photographic erythema improvement (mean %)					
Multiplexed PDL/Nd:YAG	10–50	10–50	10–50	10–50	–
PDL	10–50	10–50	10–50	10–50	–
Spectrophotometer erythema index (mean ± SD)					
Multiplexed PDL/Nd:YAG at Point A	526.7 ± 127.9	537.3 ± 111.4	542.1 ± 97.2	537.0 ± 103.9	0.585
Multiplexed PDL/Nd:YAG at Point B	591.9 ± 96.9	559.0 ± 113.0	559.7 ± 111.2	537.7 ± 93.6	0.002
Multiplexed PDL/Nd:YAG at Point C	520.1 ± 119.7	509.2 ± 95.2	498.1 ± 116.7	465.7 ± 114.6	0.007
PDL at Point A	534.7 ± 113.2	526.4 ± 106.1	550.6 ± 85.4	525.9 ± 91.5	0.287
PDL at Point B	585.6 ± 99.4	575.4 ± 85.0	563.2 ± 85.1	537.6 ± 97.8	0.004
PDL at Point C	520.5 ± 95.5	497.0 ± 91.3	494.3 ± 96.3	465.2 ± 99.9	0.005
Pain during treatment (0 to 10)					
Multiplexed PDL/Nd:YAG	–	5.11 ± 2.6	5.0 ± 2.5	5.04 ± 3.0	0.948
PDL	–	5.93 ± 2.9	5.89 ± 2.4	5.33 ± 2.9	0.253
Pain during first 3 days (0 to 10)					
Multiplexed PDL/Nd:YAG	–	1.59 ± 2.0	1.74 ± 2.0	1.67 ± 2.2	0.894
PDL	–	3.41 ± 3.0	2.89 ± 2.7	2.44 ± 3.2	0.202
Side effects observed (*n*, %)					
Multiplexed PDL/Nd:YAG	–	4 (14.8)	7 (25.9)	9 (33.3)	–
PDL	–	15 (55.6)	15 (55.6)	13 (48.1)	–
Purpura in first week after treatment (0 to 100%)					
Multiplexed PDL/Nd:YAG	–	20.74 ± 27.2	26.15 ± 27.1	27.0 ± 25.1	0.122
PDL	–	63.70 ± 21.3	51.92 ± 24.2	57.41 ± 27.7	0.063
Global satisfaction with treatment (0 to 100%)					
Multiplexed PDL/Nd:YAG	–	56.15 ± 27.7	61.85 ± 27.7	67.8 ± 22.2	0.046
PDL	–	46.54 ± 26.2	59.26 ± 23.2	61.85 ± 20.0	0.001
Recommendation of this treatment to a friend (n, %)					
Multiplexed PDL/Nd:YAG	–	22 (81.5)	23 (85.2)	26 (96.3)	–
PDL	–	17 (63.0)	19 (70.4)	20 (70.4)	–

SD = standard deviation, PDL = pulsed dye laser, Nd:YAG = neodymium:yttrium-aluminum-garnet laser.

photometer measurement (MAC), and laser treatment (NM), and that PV and MAC were blinded to which side of the face received PDL or multiplexed PDL/Nd:YAG modality.

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. Spectrophometric 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.

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼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. **Odmerjanje 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 po 16 tednih 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 dveh skupinah niso preučevali. Varnosti in učinkovitosti zdravila pri otrocih in mladostnikih, mlajših od 18 let, niso ugotovili. **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 katero koli klinično pomembno aktivno okužbo se zdravljenja ne sme uvesti, dokler okužba ne izzveni oziroma ni ustrezno zdravljena. Pred začetkom zdravljenja z guselkumabom je treba bolnike pregledati in opraviti preiskave na prisotnost tuberkuloze. Bolnike, ki prejemajo to zdravilo je treba med in po zaključku zdravljenja z guselkumabom spremljati glede znakov in simptomov aktivne tuberkuloze. Pri bolnikih z latentno ali aktivno tuberkulozo v anamnezi, ki nimajo dokumentiranega ustreznega poteka zdravljenja, je treba pred začetkom zdravljenja razmisliti o zdravljenju tuberkuloze. Če se pojavi resna preobčutljivostna reakcija, je treba zdravljenje z guselkumabom prekiniti in bolniku uvesti ustrezno zdravljenje. Bolniki, ki prejemajo to zdravilo, ne smejo sočasno prejeti živih cepiv. O odzivu na živa oziroma inaktivirana cepiva ni podatkov. Pred cepljenjem z živimi virusnimi ali bakterijskimi cepivi je treba zdravljenje z guselkumabom odložiti za najmanj 12 tednov po zadnjem odmerku in ga nato ponovno uvesti najmanj 2 tedna po cepljenju. Upoštevati je treba dodatne informacije in smernice o sočasni uporabi imunosupresivnih zdravil po cepljenju. **Interakcije:** Interakcije med guselkumabom in različnimi substrati CYP (CYP3A4, CYP2C9, CYP2C19, CYP2D6 in CYP1A2) niso verjetne. Pri sočasnem odmerjanju guselkumaba in substratov CYP450 odmerka ni treba prilagajati. Varnosti in učinkovitosti zdravila Tremfya v kombinaciji z imunosupresivi, vključno z biološkimi zdravili ali fototerapijo, niso ocenili. **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 nosečnicah ni podatkov. Iz previdnostnih razlogov se je med nosečnostjo uporabi zdravila bolje izogibati. Ni znano, ali se guselkumab izloča v materino mleko pri človeku. Odločiti se je treba, ali naj mati med zdravljenjem in do 12 tednov po njem preneha dojiti ali naj se raje preneha zdraviti z zdravilom, ob upoštevanju koristi dojenja za otroka in koristi zdravljenja za mater.Vpliva guselkumaba na plodnost pri ljudeh niso ovrednotili. **Neželeni učinki:** okužbe zgornjih dihal, gastroenteritis, okužbe z virusom Herpes simplex, dermatofitije, glavobol, diareja, urtikarija, artralgija, eritem in bolečina na mestu injiciranja (vsi NU so opisani v povzetku glavnih značilnosti zdravila). **Imetnik DzP:** Janssen-Cilag International NV, Turnhoutseweg 30, 2340 Beerse, Belgija,**Predstavništvo imetnika DzP v Sloveniji:** Johnson & Johnson d.o.o., Šmartinska cesta 53, Ljubljana **Način in režim izdajanja zdravila:** Rp/Spec. **Datum zadnje revizije besedila:** 26. 11. 2018

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

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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*

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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

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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 (1).

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 over 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.**

Age (years)	*n*	%
‹ 10	2	0.9
11–20	42	19.1
21–30	49	22.3
31–40	58	26.4
41–50	41	18.6
51–60	23	10.4
› 60	5	2.3
Total	220	100.0

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

Leprosy type	Males		Females		Total	
	n	%	n	%	n	%
TT	10	4.5	2	0.9	12	5.4
BT	38	17.3	9	4.1	47	21.4
BB	6	2.7	3	1.4	9	4.1
BL	48	21.8	36	16.4	84	38.2
LL	40	18.2	22	10.0	62	28.2
Other	6	2.7	0	0.0	6	2.7
Total	148	67.3	72	32.7	220	100.0

TT = tuberculoid leprosy, BT = borderline tuberculoid, BB = mid-borderline, BL = borderline lepromatous, LL = lepromatous leprosy.

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

Leprosy type	Rural		Urban		Total	
	n	%	n	%	n	%
TT	6	2.7	6	2.7	12	5.4
BT	16	7.3	31	14.1	47	21.4
BB	6	2.7	3	1.4	9	4.1
BL	52	23.6	32	14.5	84	38.2
LL	33	15.0	29	13.2	62	28.2
Other	2	0.9	4	1.8	6	2.7
Total	115	52.3	105	47.7	220	100.0

TT = tuberculoid leprosy, BT = borderline tuberculoid, BB = mid-borderline, BL = borderline lepromatous, LL = lepromatous leprosy.

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 93 (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.

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). Although leprosy has been associated with male gender since the sulfone era (11), the much greater incidence among males in our study might be attributed to their greater mobility and increased accessibility to healthcare (12). The number of patients from rural areas slightly outnumbered people from urban areas. A study from the western Indian state of Maharashtra found that the prevalence of the disease and number of new cases was greater in urban areas (13). This disparity of findings can best be explained by the large proportion of rural patients that our hospital attracts

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 defaulters in our study was 2.7%. Good counselling 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.

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Combination of CO2 laser therapy and curettage for sebaceous gland hyperplasia

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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 CO_2 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: CO_2 laser therapy, sebaceous gland hyperplasia

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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).

CO_2 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 CO_2 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 CO_2 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, CO_2 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 CO_2 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

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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.

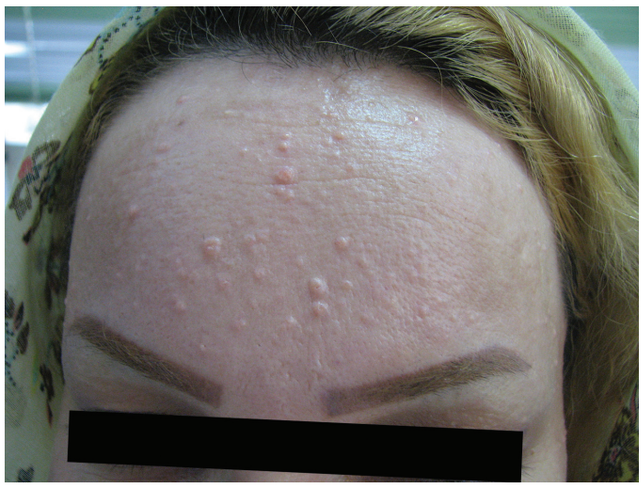

Figure 1 | Patient with frequent sebaceous hyperplasia lesions.

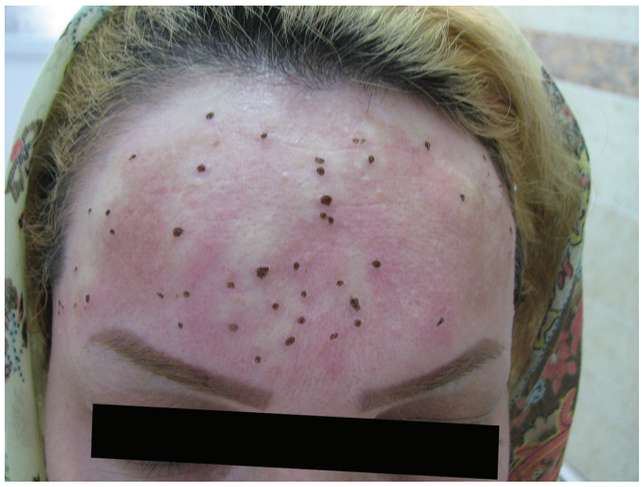

Figure 2 | Sebaceous hyperplasia lesion treated with curettage and CO_2 laser.

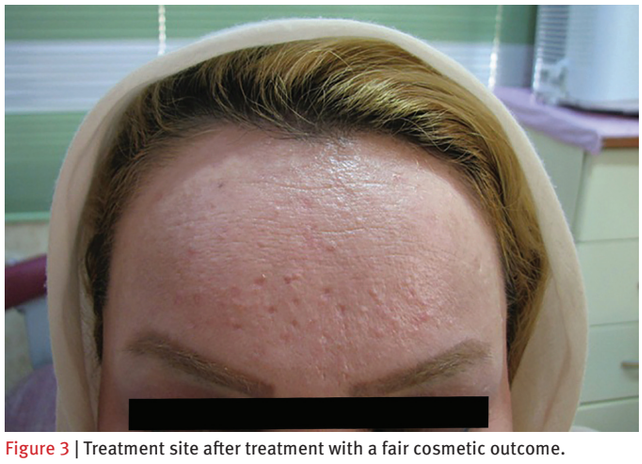

Figure 3 | Treatment site after treatment with a fair cosmetic outcome.

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).

Table 1 | Demographic and clinical characteristics of patients and outcome of CO_2 laser therapy.

Variables	*n* (%) or *mean ± SD*
Sex	
Female	32 (69.6%)
Male	14 (30.4%)
Mean time of age (years)	39.91 ± 5.69
Skin type	
Type II	9 (19.6%)
Type III	32 (69.6%)
Type IV	5 (10.9%)
Severity of lesions	
Limited	5 (10.9%)
Moderate	12 (26.1%)
Frequent	24 (52.2%)
Very frequent	5 (10.9%)
Mean time of repair (days)	11.48 ± 1.9
Cosmetic outcome	
Fair	35 (76.1%)
Moderate	9 (19.6%)
Poor	2 (4.3%)

SD = standard deviation.

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).

Table 2 | **Results of cosmetic outcome and repair time by variable.**

Variables	Cosmetic outcome (n, %)					Repair time	
	Fair	Moderate	Poor	Total	*p* value	Days	*p* value
Sex							
Female	30 (93.8)	2 (6.6)	0 (0.0)	32	0.001	10 ± 1.64	0.001
Male	5 (37.7)	7 (50.0)	2 (14.3)	14		13.07 ± 1.49	
Skin type							
Type II	8 (88.9)	1 (11.1)	0 (0.0)	9	0.001	11.11 ± 2.36	0.709
Type III	27 (84.4)	5 (15.6)	0 (0.0)	32		11.5 ± 1.84	
Type IV	0 (0.0)	3(60.0)	2 (40.0)	5		12 ± 1.58	
Severity of lesions							
Limited	4 (80.0)	1 (20.0)	0 (0.0)	5	0.767	9.2 ± 1.3	< 0.001
Moderate	10 (83.3)	2 (16.7)	0 (0.0)	12		11 ± 1.85	
Frequent	18 (75.0)	4 (16.7)	2 (8.3)	24		11.71 ± 1.57	
Very frequent	3 (60.0)	2 (40.0)	0 (0.0)	5		13.8 ± 1.09	

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 hyperpigmentation (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 CO_2 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-inflammatory hyperpigmentation after CO_2 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 CO_2 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 CO_2 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 CO_2 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 CO_2 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 CO_2 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 shrunken 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.

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

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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

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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);

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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 infers 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 1:1.13. 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 winters (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.

Table 2 | **Distribution of patients with pityriasis rosea by month, meteorological data, and Ns1Ag and/or IgM/IgG antibody positivity.**

Month	Patients	Average temperature (°C)	Average precipitation (mm)	Cases with Ns1Ag and/or IgG/IgM antibody positivity (only documented cases)
January	14	17.5	12	3
February	7	19.5	16	0
March	1	23.3	60	0
April	0	26.0	141	0
May	5	26.8	278	1
June	3	28.1	315	0
July	2	28.9	313	2
August	1	29.0	261	0
September	25	28.6	181	8
October	17	26.2	100	9
November	36	22.5	15	11
December	28	18.7	6	4
Total	136	–	–	38

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 $\hat{y} = -0.05421X + 19.25344$ (Fig. 1b). Our interpretation is that increased rainfall was associated with decreased PR incidence.

The results from linear regression plots were further analyzed for Pearson's coefficient, and we found that the monthly incidence of PR is significantly associated with months with less rainfall ($R = -0.55$, $p = 0.0001$). Such an incidence is also associated with the colder months, although the association is insignificant ($R = -0.38$; $p = 0.23$).

PR and dengue incidence

The regression equation for Y (where X = incidence of Ns1Ag-positive dengue cases per month and Y = incidence of PR per month) is $\hat{y} = 2.68596X + 3.0778$.

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.**

Study	Location	PR patients	Male:female	Seasonal variation
Harman et al. (1998)	Eastern Anatolia, Turkey	399	1:1.21	Peak during spring, autumn, and winter
Nanda et al. (1999)	Kuwait	117	1:1.38	Not reported
Tay et al. (1999)	Singapore	368	1.19:1	No variation
Traore et al. (2001)	Burkina Faso	36	Not reported	Not reported
Chuh et al. (2003)	Hong Kong	41	1:1.05	February, July, April
Chuh et al. (2005)	Minnesota, United States, Kuwait, and Diyarbakır, Turkey	1,379	Not reported	Clusters found but did not mention the seasons
Sharma et al. (2010)	Uttar Pradesh, India	200	2:1	September to December
Ayanlowo et al. (2010)	Lagos, Nigeria	427	1:1.55	October, August, March
Ganguly et al. (2013)	Southern India	73	Male preponderance	No variation
This study (2018)	Northeast India	136	Female preponderance	September to January

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).

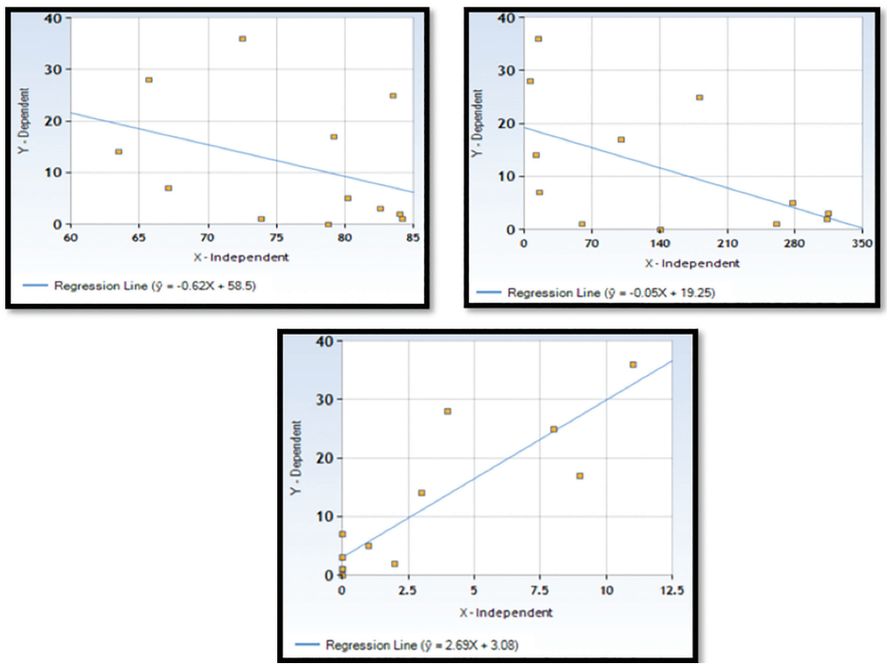

Figure 1 (clockwise) | 1a: Temperature and pityriasis rosea (PR) incidence, 1b: rainfall and PR incidence, 1c: PR and dengue incidence.

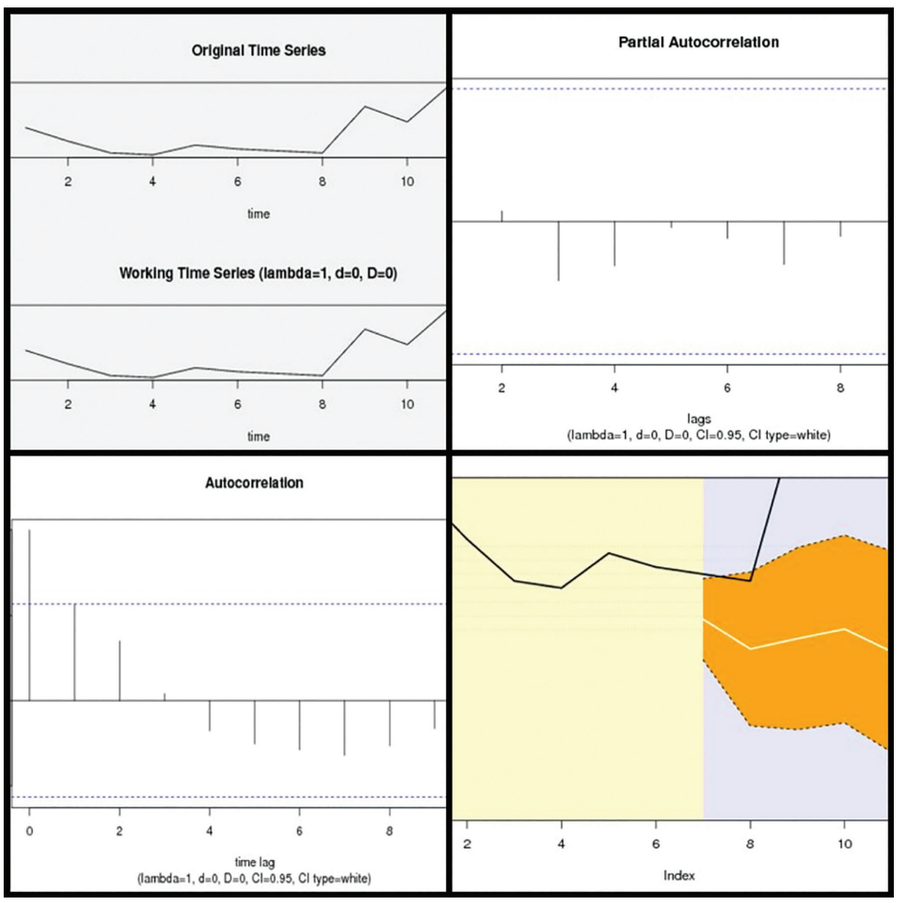

Figure 2a, b, c, d (clockwise) | Original, partial autocorrelation function, and autocorrelation function plots for pityriasis rosea (PR) incidence derived from original time series after prewhitening and SARIMA extrapolation forecast for PR incidence.

b) SARIMA forecast for PR incidence:
For prewhitening, the model SARIMA (p = 1, d = 0, q = 0, P = 2, D = 1, Q = 2 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 Ns1Ag 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% confidence interval (CI) = 1.294 to 4.4061; RR = 2, 95% CI = 1.217 to 3.2868; Yates x^2 = 7.19 p = 0.0073; two-tailed Fisher's exact probability test p = 0.00698), 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 B19, 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 136 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-

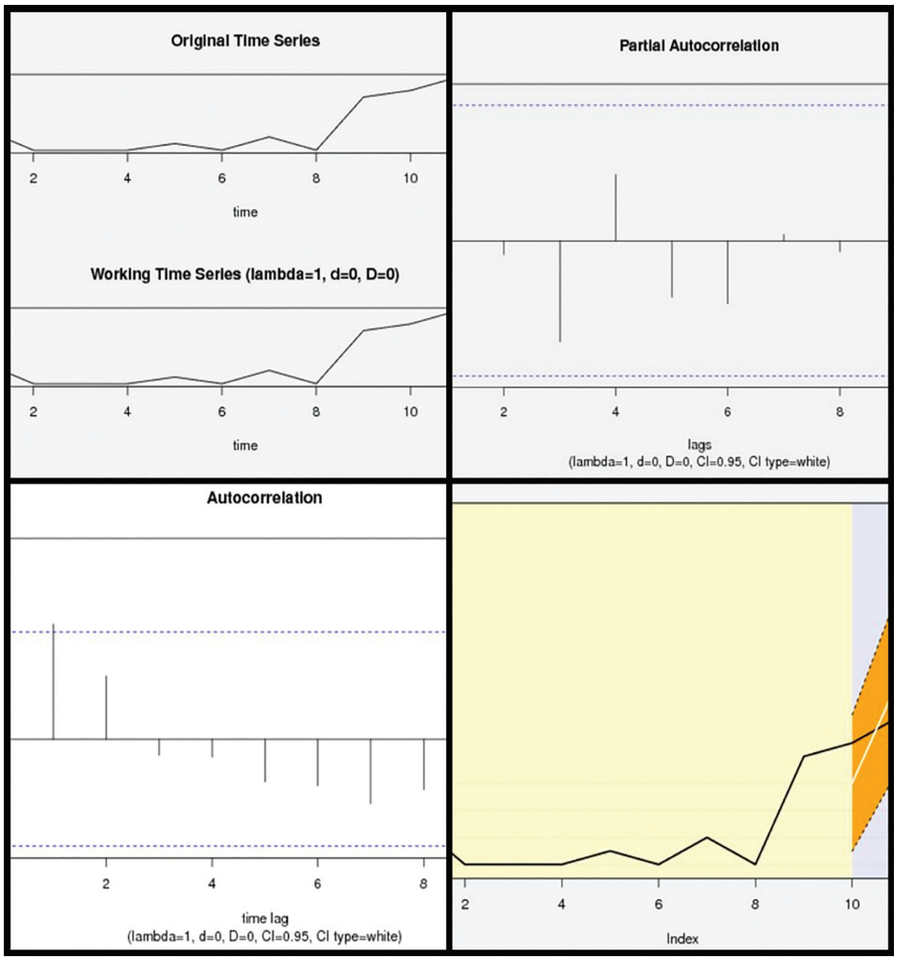

Figure 3a, b, c, d (clockwise) | Original, partial autocorrelation function, and autocorrelation function plots for preceding history of NsAg1 and/or IgG or IgM positivity and SARIMA extrapolation forecast for pityriasis rosea cases with preceding dengue history.

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 Chuh et al., there is another proposed classification of PR by Drago 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.

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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:

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

where n is the total number of samples, x_i (x_1, x_2, . . . , 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, 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) × (P, D, Q)S, 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) $\Phi(B^S)\varphi(B)(x_t - \mu) = \Theta(B^S)\theta(B)w_t$

The non-seasonal components are:
AR: $\varphi(B) = 1 - \varphi_1 B - \ldots - \varphi_p B^p$
MA: $\theta(B) = 1 + \theta_1 B + \ldots + \theta_q B^q$

The seasonal components are:
Seasonal AR: $\Phi(B^S) = 1 - \Phi_1 B^s - \ldots - \Phi_P B^{PS}$
Seasonal MA: $\Theta(B^S) = 1 + \Theta_1 B^s + \ldots + \Theta_Q B^{QS}$

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.

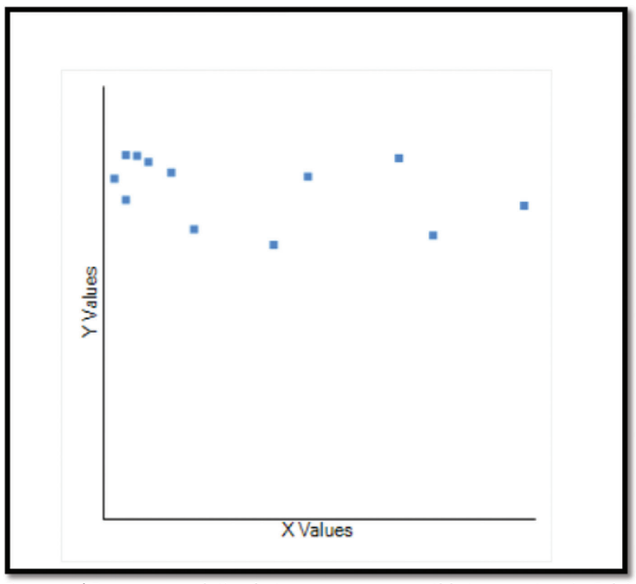

Figure 1s | Pearson correlation between average monthly temperature in Celsius and pityriasis rosea cases: $R = -0.3762$. (The p-value is 0.22837. The result is not significant at $p < 0.05$.).

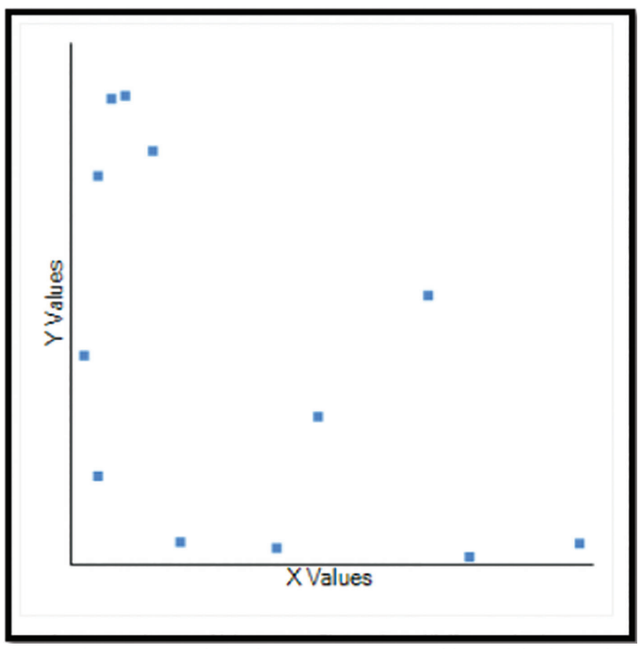

Figure 2s | Pearson correlation between average monthly precipitation and incidence of pityriasis rosea ($R = -0.5458$). This is a moderate negative correlation, which means there is a tendency for increased incidence ($p = 0.0001$). The value of R^2, the coefficient of determination, is 0.2979.

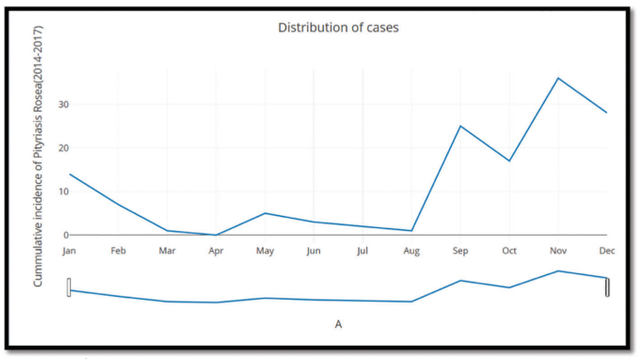

Figure 3s | Plot between average monthly precipitation and incidence of pityriasis rosea.

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Pulsed-dye laser versus intralesional *Candida albicans* antigen injection in treatment of genital warts

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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

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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 intralesional immunotherapeutic antigens have also been tried, such as *Candida albicans* (*C. albicans*) antigen, tuberculin antigens (including purified protein derivative, *Mycobacterium w* vaccine, and Bacillus Calmette–Guérin), 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 cytotoxic 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

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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 VasQ, 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, immunosupression, 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).

Characteristics	Group I (n = 20)	Group II (n = 20)	Statistical test	p-value
Age (years), mean ± SD	31.9 ± 11.6	31.95 ± 11	Student's t 0.014	0.99
Sex			Fisher's exact	
Female	19 (95%)	13 (65%)	5.6	0.04
Male	1 (5%)	7 (35%)		
Number of lesions			Fisher's exact	
1–5	10 (50%)	6 (30%)	2.07	0.35
6–10	3 (15%)	6 (30%)		
› 10	7 (35%)	8 (40%)		
Duration of current lesions, months, mean ± SD	4.3 ± 3.9	5.9 ± 6.3	Student's t 0.97	0.33
Distribution of current lesions			MC	
External genital	20 (100%)	20 (100%)	11	0.03
Perianal	4 (20%)	4 (20%)		
Intraanal	0	0		
Internal genital	0	3 (15%)		
Vaginal	0	2 (10%)		
Cervical	0	1 (5%)		
Other partner affected			Fisher's exact	
Yes	5 (31%)	6 (40%)	1.201	0.6
No	11 (69%)	14 (60%)		
Previous treatment			MC	
No	18 (90%)	18 (90%)	2	1.0
Ablative CO_2 laser	1 (5%)	0 (0%)		
Cryotherapy	1 (5%)	1 (5%)		
Electrocautery	0	1 (5%)		
Number of sessions needed for best results, mean ± SD (median)	2.1 ± 0.9 (2)	2.7 ± 0.7 (3)	MC 12.5	0.001*
Response to treatment after three sessions			MC	
Excellent improvement	19 (95%)	10 (50%)	13.3	0.001*
Marked improvement	1 (5%)	2 (10%)		
Moderate improvement	0 (0%)	1 (5%)		
Mild improvement	0 (0%)	2 (10%)		
No/poor improvement	0 (0%)	5 (25%)		
Side effects (present/absent)				
Pain	15 (75%) / 5 (5%)	9 (45%) / 11 (55%)		
Edema	–	17 (85%) / 3 (15%)	–	–
Dyspigmentation	1 (5%) / 19 (95%)	1 (5%) / 19 (95%)		
Flu-like symptoms	–	17 (85%) / 3 (15%)		

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

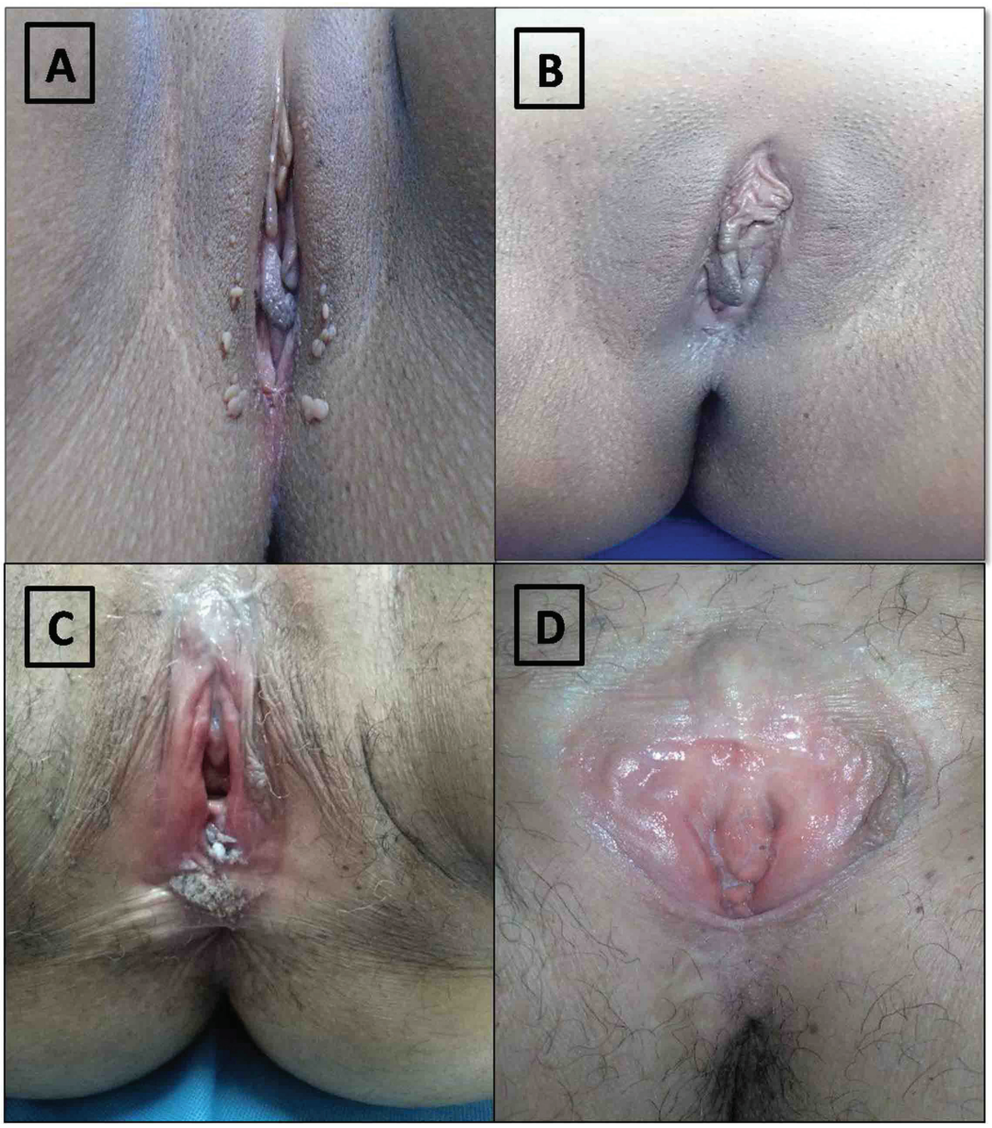

Figure 1 | A: a 22-year-old female patient with multiple genital warts involving both the labia majora and perineum. B: after two sessions of pulsed-dye laser (PDL) with excellent improvement. C: a 46-year-old female patient with multiple genital warts involving the perineum and vestibular fossa. D: after two sessions of PDL with excellent improvement.

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.

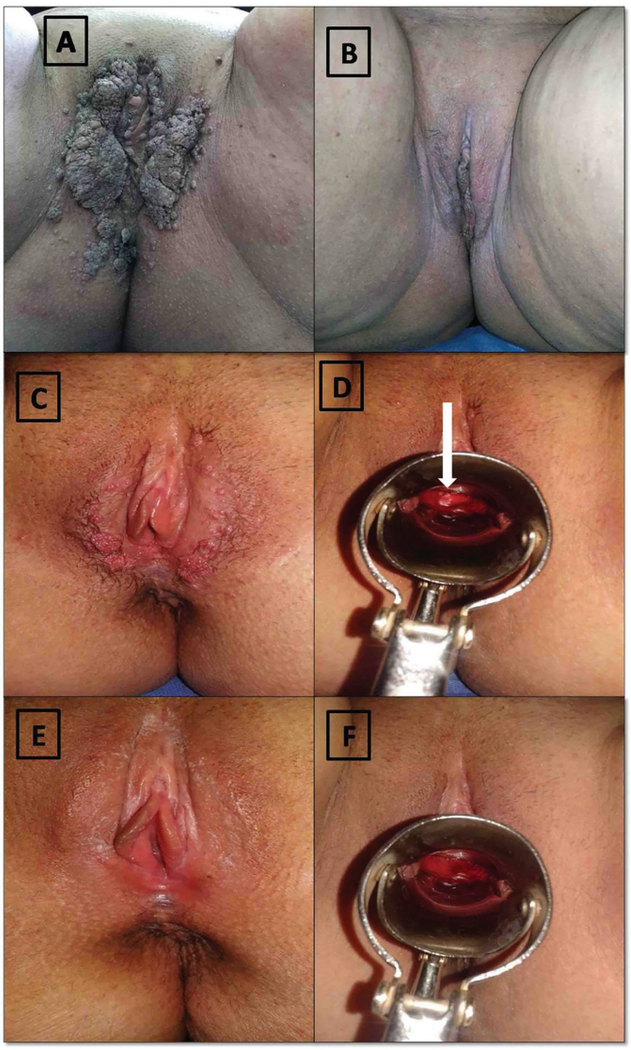

Figure 2 | A: a 51-year-old female patient with genital warts involving the entire vulva. B: after three injection sessions of *Candida albicans* antigen with excellent improvement. C: a 26-year-old female patient with multiple genital warts on the labia majora. D: wart on cervical os (arrow) in the same patient. E and F: after two injection sessions of *C. albicans* antigen with excellent improvement of both external and uninjected internal warts.

Discussion

Primary treatment modalities for warts include destructive therapies such as cryotherapy, electrocautery, laser therapy, and surgical excision. They are designed to damage and remove an apparent skin lesion rather than to kill the virus, for which they lack any specific antiviral effect. This is a major drawback for patients in whom the adjacent, clinically normal skin harbors viral DNA, and thus they are at great risk of recurrence and transmitting the infection. In addition, these therapies are mostly associated with pain, incomplete cures, and disfiguring scarring in addition to the high rates of recurrence (14, 15). PDL showed efficacy in several non-vascular indications, including simple and recalcitrant verrucae vulgaris, on various sites of the body using various fluencies ranging from 6 to 10 J/cm² without ablation (16, 17).

The results of this study detected an overall response rate of 95% for all warts treated with PDL after three treatment sessions. The required number of sessions and the response rates varied by the size and surface area of the warts. Only one patient (5%) did not achieve complete clearance after the third session and needed an additional session to achieve a complete response.

In a previous study including 22 patients with genital warts using a 585 nm PDL with a fluence of 6 to 7 J/cm², all patients achieved complete resolution after an average of 1.59 treatment sessions (range: one to five sessions) with a 2- to 3-week interval. A single treatment session was sufficient in 59% of the patients (18).

Badawi et al. (19) used 585 nm PDL in the form of three to four overlapping pulses with higher fluencies (9 to 10 J/cm²) to treat 174 male patients with anogenital warts, and they reported a 96% complete clearance rate. This was achieved after one to three sessions with 2-week intervals between. In this study, seven to 10 overlapping pulses were applied at every site treated, based on the size and thickness of the warts, until the appearance of a faint livid color. This multi-pass technique makes possible greater target destruction while preserving laser selectivity.

It should be considered that pulse stacking makes it possible to apply cumulative heating of the dermal capillaries with concomitant epidermal cooling between pulses due to a shorter epidermal thermal relaxation time than that of dermal capillaries (20, 21).

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 Komericki 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 *C. albicans* antigen immunotherapy. The results of this study and several others revealed partial or no response in some subjects to *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 *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 *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 *C. albicans* antigen immunotherapy reported in our study. This finding has also been reported by other investigators utilizing intralesional 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 over 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 intralesional antigen immunotherapy (30, 31).

Considering the oncogenic potential of some HPV strains affecting the genital area, an additional anti-oncogenic role of *C. albicans* antigen immunotherapy might be suggested. Because of the immune-enhancing capability of recall antigens such as the *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 *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, *C. albicans* antigen immunotherapy was found to induce a significant polarization of Th1 response with production of IFN-γ, which indicated that *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 *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. *C. albicans* antigen injection might be helpful for treating distant uninjected warts, including troublesome internal genital ones.

This study recommends trying *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.

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Galectin 1 in dermatology: current knowledge and perspectives

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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

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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 glycoconjugates 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).

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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, cultured stromal 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, Dvorankova 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 downregulation 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 malign 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 κ-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 immunocytochemical marker for oral SCCs.

Because Gal 1 is a hypoxia-regulated protein and a prognostic marker in head and neck SSC, Koonce 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, Rappl 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 phages 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.

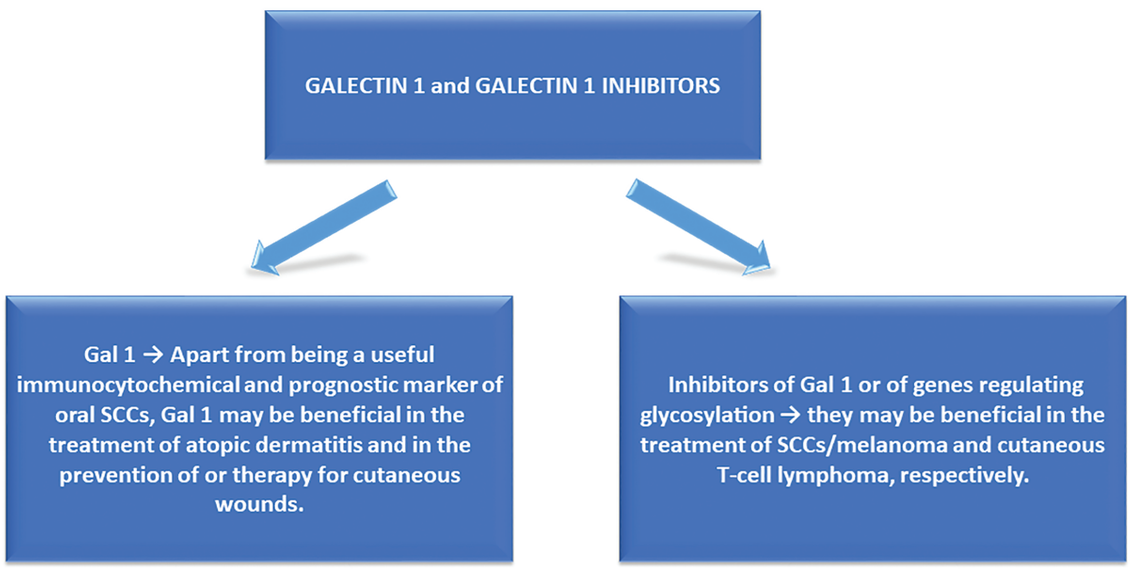

Figure 1 | Positive effects and potential therapeutic targets of Galectin 1 (Gal 1) and Gal 1 inhibitors. SCC = squamous cell carcinoma.

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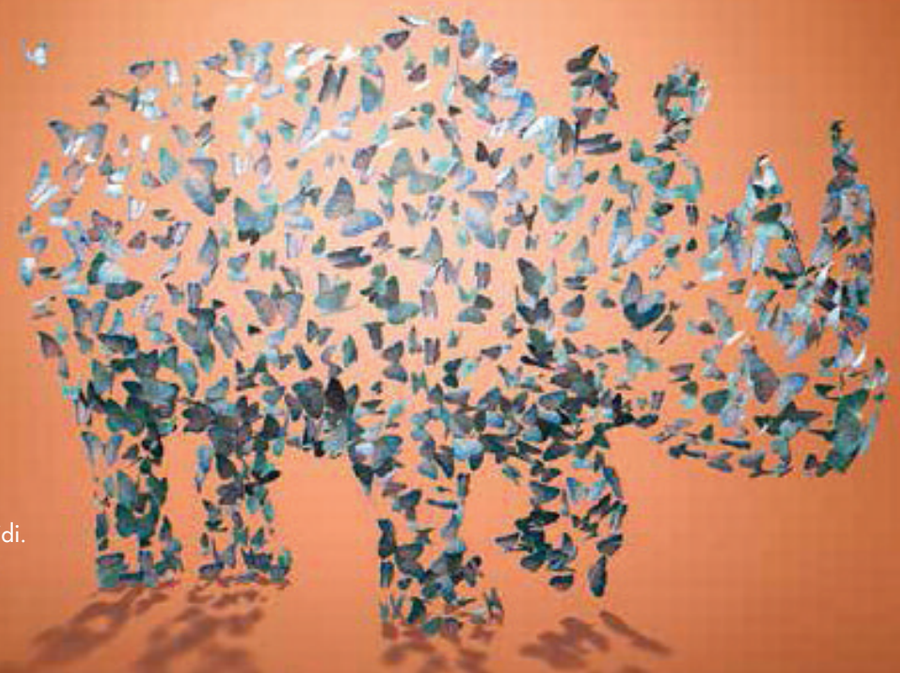

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- **psoriaza**;
- **lichen ruber planus**;
- **kronični eritematodes**;
- **vzdrževalno zdravljenje dermatoz**, ki so bile predhodno zdravljene z močnejšimi kortikosteroidi.

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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.

Odmerjanje in način uporabe
Odmerjanje je individualno in odvisno od resnosti simptomov. Zdravilo dvakrat na dan nanesemo na obolelo kožo in ga vanjo narahlo vtremo. Pri blažjih oblikah obolenj zadošča, da ga nanesemo dvakrat na dan, pri resnejših pa lahko do štirikrat na dan, vendar mora o tem odločati zdravnik. Za majhne otroke običajno zadošča nanos zdravila enkrat na dan. Priporočamo kratkotrajno zdravljenje, ne dlje od petih dni. Uporaba zdravila pod okluzivnim povojem pospeši potek zdravljenja. Okluzivni povoj lahko ostane na mestu nanosa največ tri dni. Ko se stanje izboljša, zadostuje nanos enkrat na dan ali dvakrat do trikrat na teden. Pri otrocih uporabo zdravila pod okluzivnim povojem odsvetujemo zaradi povečane absorbcije zdravila in s tem večje možnosti pojava sistemskih kortikosteroidnih reakcij. Plenice lahko delujejo kot okluzivni povoj in tako povečajo absorbcijo zdravila.

Kontraindikacije
Preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov.

Neželeni učinki Lokalni neželeni učinki zdravila so podobni kot pri drugih lokalnih kortikosteroidih.

Organski sistem	Redki > 1/10.000, < 1/1000	Zelo redki < 1/10.000	Neznana pogostnost
Imunski sistem			preobčutljivost
Endokrine žleze		motnja delovanja nadledvične žleze	
Infekcijske bolezni	sekundarne infekcije		
Koža in podkožno tkivo	atrofija kože, pogosto ireverzibilna, s tanjšanjem povrhnjice, srbenje, rozacea, suha koža, hipertrihoza, miliarija, folikulitis, teleangiektazija, purpura, kožne strije, pustularne akne, perioralni dematitis, rebound učinek,depigmentacija kože, dermatitis in ekcem, vključno s kontaktnim dermatitisom		

Posebna opozorila in previdnostni ukrepi
Pri bakterijskih in glivičnih infekcijah je treba zdravljenje kombinirati z antibiotiki ali antimikotiki. Pri uporabi zdravila na večjih površinah kože, v velikih količinah ali na občutljivejših mestih in pod okluzivnim povojem se lahko hidrokortizonbutirat absorbira skozi kožo in povzroči sistemske kortikosteroidne reakcije. Dolgotrajna uporaba lokalnih kortikosteroidov pri novorojenčkih ni priporočljiva. Prav tako ni priporočljivo dolgotrajno zdravljenje majhnih otrok, ker lahko privede do adrenalne supresije. Otroci so za lokalno inducirano supresijo osi hipotalamus-hipofiza in Cushingov sindrom občutljivejši kot odrasli zaradi večjega deleža površine kože glede na telesno maso. Izogibati se je treba dolgotrajnemu dajanju zdravila na kožo obraza in paziti, da zdravilo ne bi prišlo v oči, ker se lahko razvije glavkom ali subkapsularna katarakta.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij
Raziskav o medsebojnem delovanju niso izvedli.
Ni poročil o klinično pomembnem medsebojnem delovanju lokalnih kortikosteroidov in drugih zdravil.

Nosečnost in dojenje
Pri predpisovanju zdravila nosečnicam je potrebna previdnost.

Preveliko odmerjanje
Akutno preveliko odmerjanje pri lokalni uporabi ni možno. Pri zdravljenju večjih površin kože ali dolgotrajnem zdravljenju, posebno ob uporabi okluzivnega povoja, se lahko pojavijo sistemski učinki kortikosteroidov, in to predvsem supresija osi hipotalamus-hipofiza-nadledvična žleza, ki pa je običajno reverzibilna. Znaki so Cushingov sindrom, hiperglikemija in glukozurija. Zdravljenje je simptomatsko.

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Trichotillomania: a psychopathological perspective and the psychiatric comorbidity of hair pulling

Sarah Anwar[1], Mohammad Jafferany[2] ✉

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

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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). A thorough clinical exam and trichoscopy are the main methods for diagnosing trichotillomania.

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

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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, without 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 asymmetrical 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 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 (15). 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 judgement 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-acetylcysteine 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-acetylcysteine 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.

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

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Abstract

A 72-year-old female patient presented with an end-stage renal disease on on-line hemodiafiltration and warfarin therapy 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

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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, methyldigoxin, sevelamer, cinacalcet, tizanidine, rosuvastatin, pantoprazole, sertraline, bromazepam, tramadol, and paracetamol.

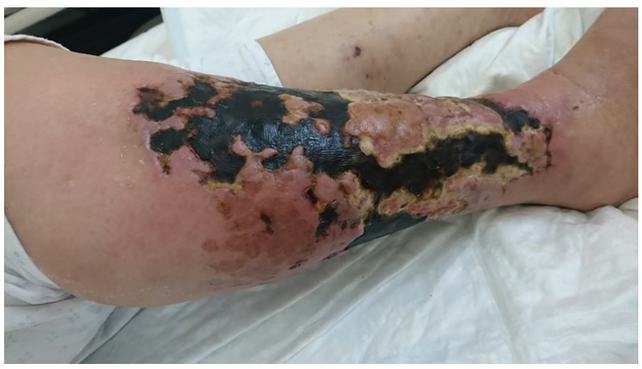

Figure 1 | Necrotic ulcers on both shins with livedo racemosa on the peripheral skin. Large and hard subcutaneous plaques are located on the shins and thighs (Alen Jovic, Department of Dermatovenerology, Maribor University Medical Center).

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,

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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).

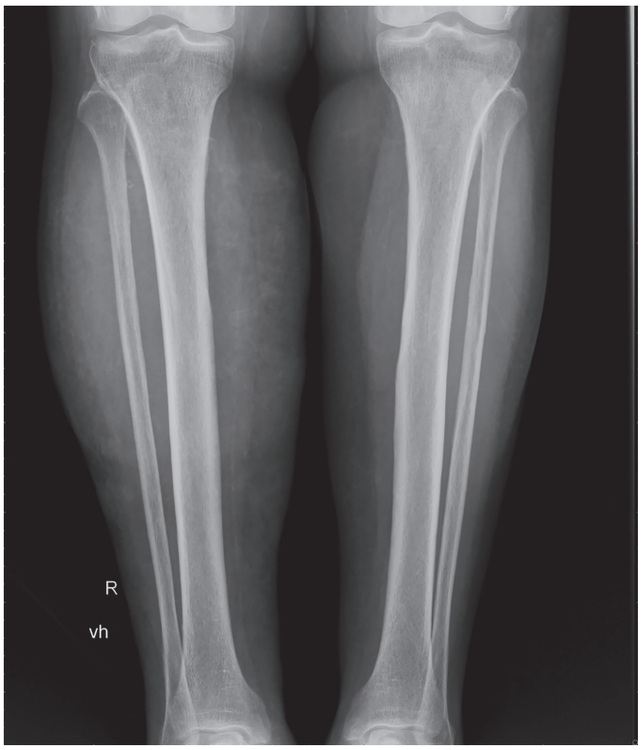

Figure 2 | Radiographic imaging of both shins, demonstrating moderate skin calcifications (Department of Radiology, Maribor University Medical Center).

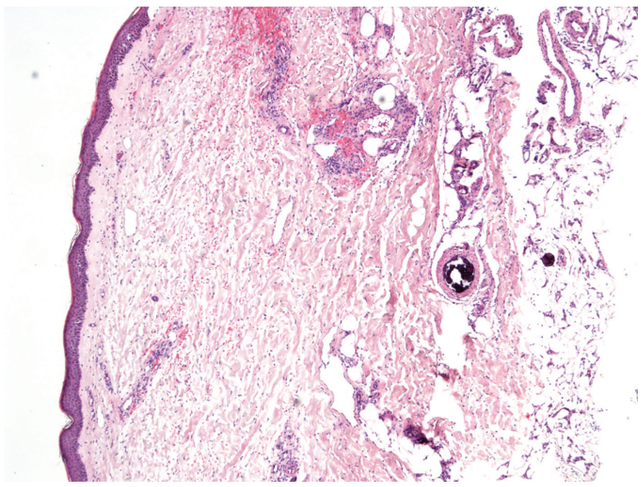

Figure 3 | Histopathological examination of a skin biopsy taken from the edge of ulceration, showing characteristic calcification, thrombosis, and fibro-intimal hyperplasia of dermal and subcutaneous arterioles (Institute of Pathology, Faculty of Medicine, University of Ljubljana).

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 buprenorphine transdermal patch. Due to the burning character of the pain, pregabalin was added. Off-label treatment with sodium thiosulfate (STS) was initiated with one intralesional 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.

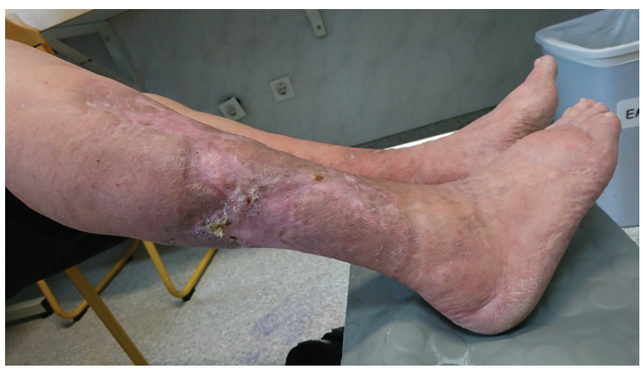

Figure 4 | Completely healed ulcers and dissolved subcutaneous plaques on the shins after 8 months of multidisciplinary treatment of advanced uremic calciphylaxis (intravenous sodium thiosulfate, regulation of calcium and phosphate homeostasis, discontinuation of warfarin, analgesia, treatment of cellulitis, and careful wound care; Vesna Breznik, Department of Dermatovenerology, Maribor University Medical Center).

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 $Na_2O_3S_2$ or $Na_2S_2O_3$) is the most common drug being used off-label to treat calciphylaxis, primarily used for the treatment of cyanide poisoning and urolithiasis, 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, intravenous during HD sessions, oral, intraperitoneal, intralesional, 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 hypernatremia, headache, hypotension, 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, intraperitoneal, 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 tumoral CC (29, 30).

Conclusions

In the case presented of a patient with uremic calciphylaxis with extensive and ulcerated lesions on the lower extremities, complicated 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 management, 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 physicians and other professionals from various medical fields.

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Isolated collagenoma on the face: a rare occurrence

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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

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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 extracellular 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, back, and palmo-plantar areas. One case each was seen on the frontal area and labia majus (Table 1). Comprehensive search of the literature yielded no descriptions of isolated collagenoma on the face to date.

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

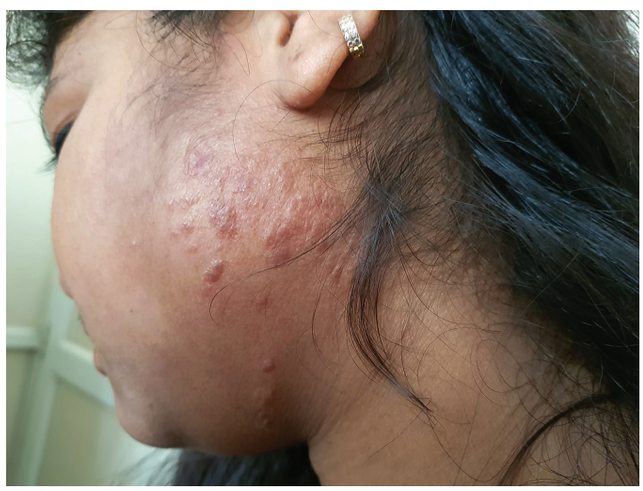

Figure 1 | Multiple skin-colored papules varying from 2 mm to 10 mm in size on the left side of face.

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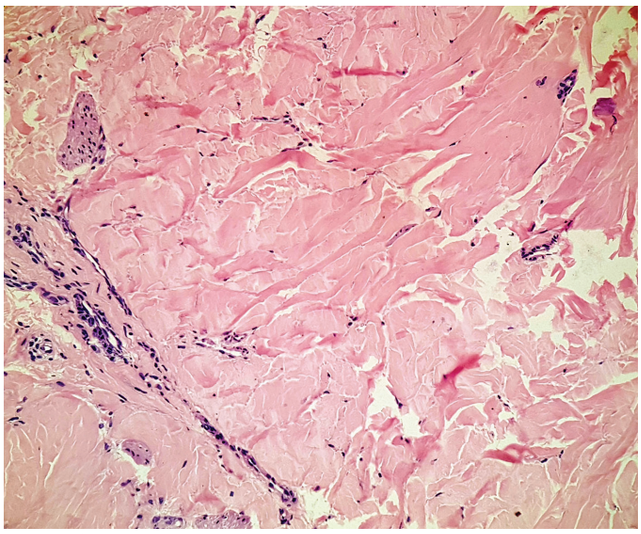

Figure 2 | Acellular, thickened, and condensed collagen in a haphazard arrangement in the reticular dermis (H&E, 200×).

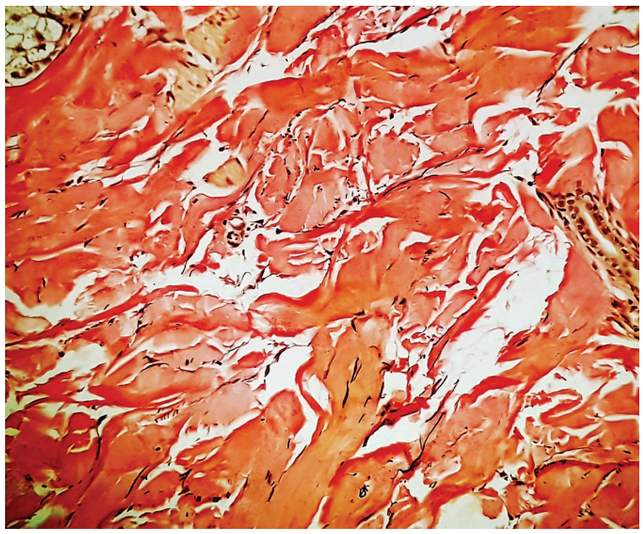

Figure 3 | Fragmented, curled, and denatured elastic fibers in the dermis (VVG, 400×).

Table 1 | Eighteen cases of isolated collagenoma.

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

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 papulolinear 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.

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* 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]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti.

Taltz 80 mg raztopina za injiciranje v napolnjenem injekcijskem peresniku **Kakovostna in količinska sestava:** Ena napolnjen injekcijski peresnik vsebuje 80 mg iksekizumaba v 1 ml. Iksekizumab je rekombinantno humanizirano monoklonsko protitelo, izdelano v ovarijskih celicah kitajskega hrčka (Chinese Hamster Ovary – CHO). **Terapevtske indikacije:** Zdravilo Taltz je indicirano za zdravljenje zmerne do hude psoriaze s plaki pri odraslih, ki so primerni za sistemsko zdravljenje. Zdravilo Taltz je samo ali v kombinaciji z metotreksatom indicirano za zdravljenje aktivnega psoriatičnega artritisa pri odraslih bolnikih, ki so se nezadostno odzvali na zdravljenje z enim ali večimi imunomodulirajočimi protirevmatičnimi zdravili (DMARD) ali pa takega zdravljenja ne prenašajo. **Odmerjanje in način uporabe:** Zdravilo Taltz je namenjeno za uporabo pod vodstvom in nadzorom zdravnika, ki ima izkušnje z diagnozo in zdravljenjem bolezni, za katere je zdravilo Taltz indicirano. Odmerjanje *Psoriaza s plaki* Priporočeni odmerek je 160 mg s subkutano injekcijo (dve injekciji po 80 mg) v tednu 0, ki mu sledi 80 mg (ena injekcija) v tednih 2, 4, 6, 8, 10 in 12, nato pa vzdrževalno odmerjanje 80 mg (ena injekcija) vsake 4 tedne. *Psoriatični artritis* Priporočeni odmerek je 160 mg, dan s subkutano injekcijo (dve injekciji po 80 mg) v tednu 0, ki mu sledi odmerek 80 mg (ena injekcija) vsake 4 tedne po tem. Za bolnike s psoriatičnim artritisom, ki imajo sočasno zmerno do hudo psoriazo s plaki, je priporočeni režim odmerjanja enak kot za bolnike s psoriazo s plaki. Pri bolnikih, ki se po 16 do 20 tednih niso odzvali na zdravljenje, je treba razmisliti o prekinitvi zdravljenja. Pri nekaterih bolnikih z začetnim delnim odzivom se stanje ob nadaljevanju zdravljenja prek 20 tednov lahko izboljša. *Starejši (≥ 65 let)* Prilagajanje odmerkov ni potrebno. *Pediatrična populacija* Smotrne uporabe zdravila Taltz pri otrocih, mlajših od 6 let, za zdravljenje zmerne do hude psoriaze s plaki, ni. Smotrne uporabe zdravila Taltz pri otrocih, mlajših od 2 let, za indikacijo psoriatičnega artritisa ni. Način uporabe Subkutana uporaba. Zdravilo Taltz je namenjeno za subkutano injiciranje. Mesta injiciranja je mogoče spreminjati. **Kontraindikacije:** Resna preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov. Klinično pomembne aktivne okužbe (npr. aktivna tuberkuloza). **Posebna opozorila in previdnostni ukrepi:** Okužbe: Zdravljenje z zdravilom Taltz je povezano s povečano stopnjo okužb, kot so okužbe zgornjih dihalnih poti, oralna kandidaza, konjunktivitis in glivične okužbe kože. Zdravilo Taltz je treba pri bolnikih s klinično pomembnimi kroničnimi okužbami uporabljati previdno. Zdravila Taltz se ne sme dajati bolnikom z aktivno tuberkulozo (TB). Pri bolnikih z latentno tuberkulozo je treba pred začetkom zdravljenja z zdravilom Taltz razmisliti o zdravljenju proti tuberkulozi. Preobčutljivost: Poročali so o resnih preobčutljivostnih reakcijah, vključno z nekaj primeri anafilaksije, angioedema, urtikarije in, redko, resnih zapoznelih (10–14 dni po injiciranju) preobčutljivostnih reakcij, ki so vključevale široko razširjeno urtikarijo, dispnejo in visoke titre protiteles. Vnetna črevesna bolezen: Previdnost je potrebna pri predpisovanju zdravila Taltz bolnikom z vnetno črevesno boleznijo, vključno s Crohnovo boleznijo in ulceroznim kolitisom, bolnike pa je treba skrbno spremljati. Cepljenja: Zdravila Taltz se ne sme uporabljati skupaj z živimi cepivi. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij**: Varnost zdravila Taltz v kombinaciji z drugimi imunomodulatorji ali fototerapijo ni bila ovrednotena. Opravili niso nobenih formalnih študij medsebojnega delovanja zdravil in vivo. Ob uvedbi zdravljenja z iksekizumabom je treba pri bolnikih, ki prejemajo zdravila, ki se presnavljajo prek CYP450, razmisliti o terapevtskem spremljanju zdravljenja. Ob sočasnem dajanju zdravila Taltz z metotreksatom (MTX) in/ali kortikosteroidi pri bolnikih s psoriatičnim artritisom niso opazili medsebojnega delovanja zdravil. **Plodnost, nosečnost in dojenje**: Ženske v rodni dobi morajo med zdravljenjem in vsaj 10 tednov po njem uporabljati učinkovito kontracepcijsko metodo. Na voljo so le omejeni podatki o uporabi iksekizumaba pri nosečnicah. Iz previdnostnih ukrepov se je med nosečnostjo bolje izogibati uporabi zdravila Taltz. Ni znano, ali se iksekizumab izloča v materino mleko pri človeku in ali se sistemsko absorbira po zaužitju. **Neželeni učinki:** Neželeni učinki zdravila, o katerih so najpogosteje poročali, so bili reakcije na mestu injiciranja in okužbe zgornjih dihalnih poti (najpogosteje nazofaringitis). *Zelo pogosti:* okužbe zgornjih dihalnih poti, reakcije na mestu injiciranja *Pogosti:* glivične okužbe kože, herpes simpleks (mukokutani), orofaringealna bolečina, navzea *Občasni:* gripa, rinitis, oralna kandidaza, konjunktivitis, celulitis, nevtropenija, trombocitopenija, angioedem, urtikarija, izpuščaj, ekcem **Rok uporabnosti** 2 leti. **Posebna navodila za shranjevanje:** Shranjujte v hladilniku (2 °C–8 °C). Ne zamrzujte. Shranjujte v originalni zunanji ovojnini, da bo zdravilo zaščiteno pred svetlobo. Zdravilo Taltz lahko hranite zunaj hladilnika največ 5 dni, pri temperaturi, ki ne presega 30 ºC. **Imetnik dovoljenja za promet z zdravilom:** Eli Lilly Nederland BV, Papendorpseweg 83, 3528 BJ Utrecht, Nizozemska. **Datum prve odobritve dovoljenja za promet:** 25.4.2016 **Način predpisovanja:** Rp/Spec: Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Datum zadnje revizije besedila:** 25.5.2018

POMEMBNO OBVESTILO

To gradivo je namenjeno **samo za strokovno javnost.** Predpisovanje in izdaja zdravila Taltz je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. Pred predpisovanjem zdravila Taltz preberite celotni in zadnji veljavni Povzetek glavnih značilnosti zdravila Taltz.

Referenci:

1. Paul et al., Ixekizumab provides superior efficacy compared to ustekinumabover 52-weeks of treatment: results from IXORA-S, a phase 3 study, Journal of the American Academy of Dermatology (2018), doi: 10.1016/j.jaad.2018.06.039.
2. Zadnji veljavni povzetek glavnih značilnosti zdravila Taltz.

Eli Lilly farmacevtska družba, d.o.o., Dunajska cesta 167, 1000 Ljubljana, telefon 01 / 580 00 10, faks 01 / 569 17 05, www.elililly.si

PP-IX-SI-0145, 12.2.2019, Samo za strokovno javnost.

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Atrophoderma of Pasini and Pierini in a young adult: a case report

Antigona Begolli Gerqari[1]✉, Mybera Ferizi[1], Idriz Gerqari[2]

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 *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

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 and later by Pierini and Vivoli (1). At that time the disease was linked to localized scleroderma, and in 1958 it was classified as idiopathic atrophoderma (2). Youkoyama et al. discovered that the glycosaminoglycans found in atrophoderma of Pasini and Pierini were different from the ones observed in morphea (3). The exact cause of atrophoderma as described by Pasini and Pierini remains unknown (1, 4–9). It is a disease that is more common in adolescent and middle-aged females, although there have been cases described in children and in elderly patients. Furthermore, it has been reported that this disease can be contracted at birth.

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 *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, perifollicular lymphocytic infiltrate, and clumping of collagen fibers.

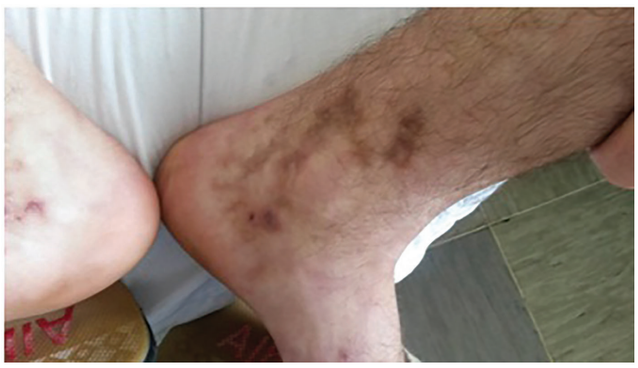

Figure 1 | Atrophoderma of Pasini and Pierini: disseminated lesions on the skin of the lower limbs.

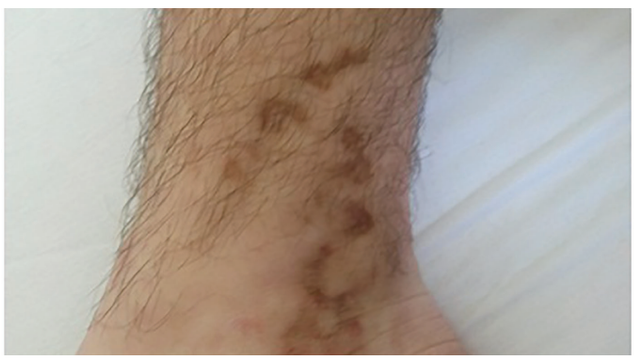

Figure 2 | Atrophoderma of Pasini and Pierini: pigmented and atrophic skin characterized by irregular borders.

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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 hyperpigmented 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 should also be prescribed (10).

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

Jordan M. Montoya[1]✉, David J. DiCaudo[1], Aaron R. Mangold[1], David L. Swanson[1]

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

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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.

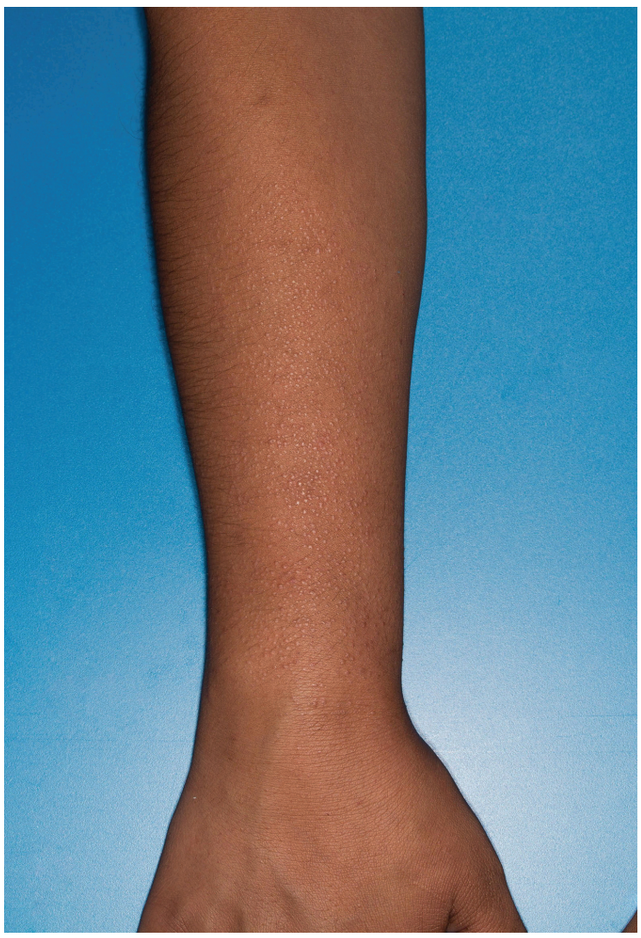

Figure 1 | Numerous monomorphic, pink papules on the dorsal forearm.

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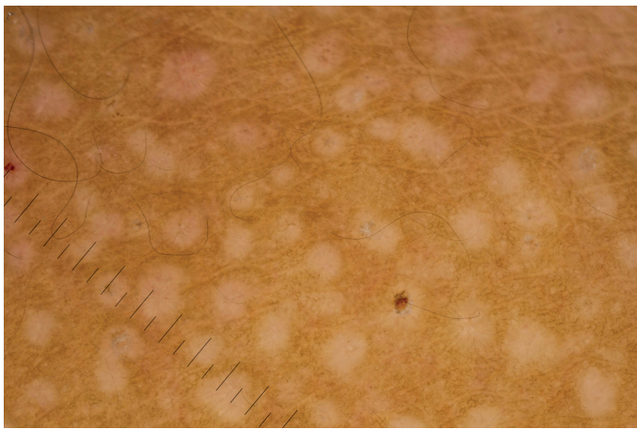

Figure 2 | Contact polarized dermoscopy of poorly marginated, white macules, some of which displayed course granularity.

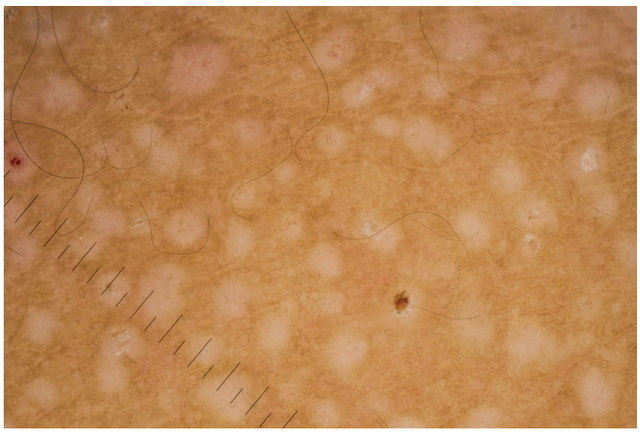

Figure 3 | Contact nonpolarized dermoscopy of poorly marginated macules with course granulations and white scales.

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.

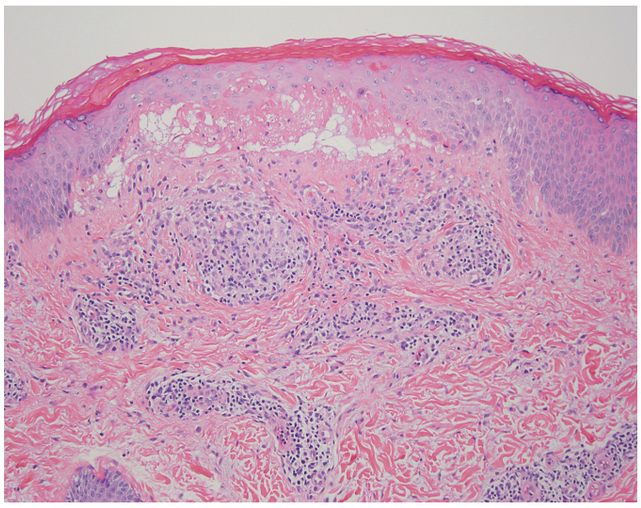

Figure 4 | Intraepidermal vesicle with focal epidermal necrosis and perivascular lymphocytic dermal inflammation (hematoxylin-eosin; original magnification 100×).

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.

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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

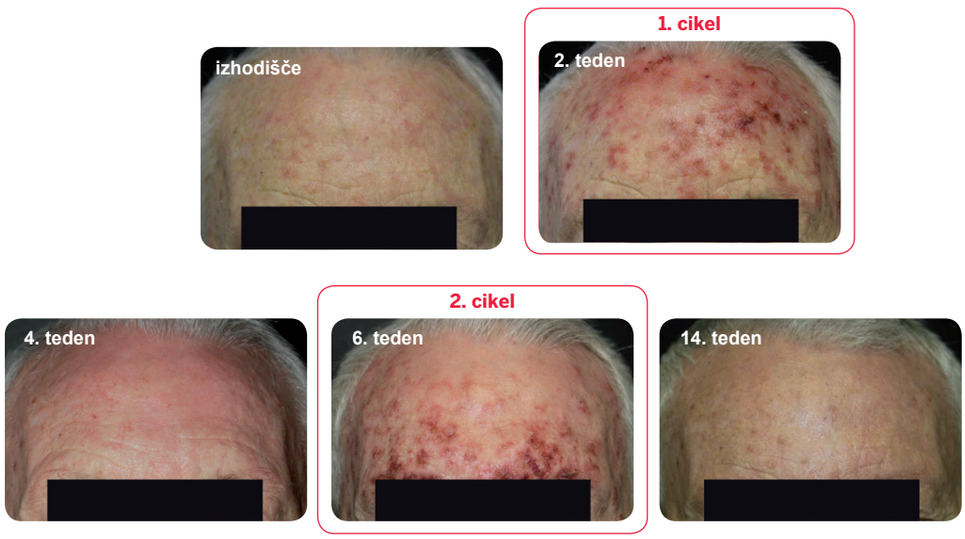
1. Akpinar Kara Y, Sarifakioglu E. Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report. Acta Dermatovenerol Alp Pannonica Adriat. 2018;27:29–31.

2. Akpinar Kara Y, Sarifakioglu E. Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report. J Turk Acad Dermatol. 2017;11:17113c1.

ZYCLARA®
imikvimod 3,75% krema

Lokalno zdravljenje aktiničnih keratoz

Učinkovito zdravljenje in zelo dober kozmetični izid po 2 ciklih zdravljenja



Povzeto po "Clinical experience of imiquimod 3.75% for actinic keratosis: results from a case series" (Tambone, S. et al. Giornale Italiano di Dermatologia e Venereologia 2018 June;153(3):333-7)

- **odkriva subklinične aktinične keratoze v obeh ciklih zdravljenja[1, 2]**
- **učinkovito in dolgotrajno odstrani subklinične in klinične lezije ne glede na njihovo število[3, 4]**
- **režim zdravljenja določa premor med dvema cikloma za omilitev kožne reakcije[1, 4]**

Skrajšan povzetek glavnih značilnosti zdravila

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. **Indikacije:** Za lokalno zdravljenje klinično značilnih, nehiperkeratoznih, nehipertrofičnih, vidnih ali otipljivih aktiničnih keratoz (AK) na celotnem obrazu ali na neporaščenem lasišču pri odraslih z normalno delujočim imunskim sistemom, kadar so drugi načini lokalnega zdravljenja kontraindicirani ali manj primerni. **Odmerjanje:** Zdravilo Zyclara (za en nanos: do 2 vrečici, 250 mg imikvimod kreme na vrečico) nanašamo enkrat na dan pred spanjem na kožo prizadetega predela v dveh dva tedna trajajočih ciklusih zdravljenja, med katerima je dvotedensko obdobje premora brez zdravljenja, če zdravnik ne odredi drugače. Predela zdravljenja sta celoten obraz ali neporaščeno lasišče. Lokalne kožne reakcije na zdravljenem predelu so do neke mere pričakovane in so zaradi načina delovanja imikvimoda pogoste. Če reakcija na imikvimod kremo povzroči prekomerno nelagodje bolnika ali če pride do hude lokalne kožne reakcije, je treba zdravljenje za nekaj dni prekiniti. V nobenem primeru pa se posameznega dvotedenskega ciklusa zdravljenja ne sme prekoračiti zaradi pozabljenih odmerkov ali obdobij prekinitve. *Okvara jeter ali ledvic:* Te bolnike je treba spremljati pod skrbnim nadzorom izkušenega zdravnika. *Pediatrična populacija:* Varnost in učinkovitost imikvimoda pri aktinični keratozi pri otrocih in mladostnikih, starih do 18 let, še nista bili dokazani. Podatkov ni na voljo. **Način uporabe:** Samo za zunanjo uporabo. Izogibati se je treba stiku z očmi, ustnicami in nosnicami. Zdravljenega predela se ne sme prevezovati ali kako drugače prekriti. 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. *Pozabljen odmerek:* Če bolnik pozabi uporabiti odmerek, naj počaka do naslednjega večera in zdravilo Zyclara uporabi takrat, nato pa naj nadaljuje z običajnim urnikom zdravljenja. Kreme se ne sme nanesti na kožo več kot enkrat na dan. Posamezen ciklus zdravljenja zaradi pozabljenih odmerkov ali obdobij prekinitve ne sme biti daljši od 2 tednov. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** *Splošna navodila za zdravljenje:* Pri lezijah, ki so atipične za AK, ali pri sumu na malignost, je potrebno opraviti biopsijo, da se določi primerno zdravljenje. Zaradi tveganja za večjo dovzetnost za sončne opekline se priporoča uporaba zaščitne sončne kreme, bolniki pa naj med zdravljenjem omejijo izpostavljanje naravni ali sončni svetlobi oziroma se mu izogibajo. Zdravljene predele kože je treba zaščititi pred sončno svetlobo. Uporaba imikvimoda ni priporočena za zdravljenje AK lezij z izrazito hiperkeratozo ali hipertrofijo, kot je na primer kožni rog. *Lokalne kožne reakcije:* Med zdravljenjem in do ozdravitve je prizadeta koža zelo verjetno videti opazno drugačna od zdrave kože. Lokalne kožne reakcije so pogoste, vendar se njihova intenzivnost med zdravljenjem navadno zmanjša oziroma po prekinitvi zdravljenja z imikvimod kremo izzvenijo. *Sistemske reakcije:* Gripi podobni znaki in simptomi lahko spremljajo burne lokalne kožne reakcije, ki lahko zajemajo utrujenost, navzeo, zvišano telesno temperaturo, mialgije, artralgije in mrazenje, ali se celo pojavijo pred njimi. V takih primerih je treba razmisliti o prilagoditvi odmerka. Bolnike z zmanjšano hematološko rezervo je treba spremljati pod skrbnim nadzorom izkušenega zdravnika. *Posebne populacije:* Bolniki z okvaro srca, jeter ali ledvic v klinične študije niso bili vključeni. Te bolnike je treba spremljati pod skrbnim nadzorom izkušenega zdravnika. *Uporaba pri bolniki z oslabljenim imunskim sistemom in/ali bolnikih z avtoimunskimi boleznimi:* Varnost in učinkovitost pri teh bolnikih nista bili ugotovljeni. Zato je treba imikvimod kremo uporabljati previdno. Pomožne snovi: Stearilalkohol in cetilalkohol lahko povzročita lokalne kožne reakcije. Benzil alkohol lahko povzroči alergične reakcije in blago lokalno draženje. Metilparahidroksibenzoat (E218) in propilparahidroksibenzoat (E216) lahko povzročita alergijske reakcije (lahko zapoznele). **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študij medsebojnega delovanja niso izvedli. To vključuje študije z imunosupresivnimi zdravili. Interakcije s sistemskimi zdravili bi bile omejene zaradi minimalne absorpcije imikvimod kreme skozi kožo. Imikvimod kremo je treba zaradi njenih imunsko-stimulativnih lastnosti previdno uporabljati pri bolnikih, ki prejemajo imunosupresivna zdravila. Sočasni uporabi zdravila Zyclara in drugih krem z imikvimodom na istem zdravljenem predelu se je treba izogibati. **Neželeni učinki:** *Zelo pogosti:* eritem, krasta, luščenje kože, kožni edem, kožne razjede, hipopigmentacija kože, eritem na mestu aplikacije, nastajanje krast na mestu aplikacije, luščenje na mestu aplikacije, suhost na mestu aplikacije, edem na mestu aplikacije, razjeda na mestu aplikacije, izcedek na mestu aplikacije. *Pogosti:* herpes simpleks, limfadenopatija, anoreksija, zvišana vrednost glukoze v krvi, nespečnost, glavobol, omotica, navzea, diareja, bruhanje, dermatitis, mialgija, artralgija, reakcija na mestu aplikacije, pruritus na mestu aplikacije, bolečina na mestu aplikacije, oteklina na mestu aplikacije, pekoč občutek na mestu aplikacije, draženje na mestu aplikacije, izpuščaj na mestu aplikacije, utrujenost, pireksija, gripi podobna bolezen, bolečine, bolečine v prsih. Ostali neželeni učinki so navedeni v Povzetku glavnih značilnosti zdravila. **Način in režim izdaje zdravila:** Rp. **Imetnik dovoljenja za promet z zdravilom:** Meda AB, Pipers väg 2, 170 73 Solna, Švedska. **Datum zadnje revizije besedila:** 08/2018

1.Zyclara Lmax Long Term Data - globalno gradivo (2015). 2. Stockfleth E et al. Eur J Dermatol 2014;24(1):23-7. 3. Hanke CW et al. J Drugs Dermatol 2011;10:165-70. 4. Peris K et al. JEADV 2014;doi:10.1111/jdv.12782.

Podatki so dostopni na lokalnem sedežu družbe in so razpoložljivi na zahtevo.

Za podrobnejše informacije prosimo glejte celoten Povzetek glavnih značilnosti zdravila,
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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

1. Retraction note: Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report. Acta Dermatovenerol Alp Pannonica Adriat. 2019;28:49.
2. Akpinar Kara Y, Sarifakioglu E. Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report. Acta Dermatovenerol Alp Pannonica Adriat. 2018;27:29–31.
3. Akpinar Kara Y, Sarifakioglu E. Inflamed bilateral linear atrophoderma of Moulin in an adult woman: a case report. J Turk Acad Dermatol. 2017;11:17113c1.
4. Kara YA. The measurement of serum tumor necrosis factor-alpha levels in patients with lichen planus. Indian J Dermatol. 2018;63:297–300.
5. Akpinar Kara Y. The measurement of serum TNF-α levels in patients with lichen planus. Acta Dermatovenerol Alp Pannonica Adriat. 2017;26:85–88.

Že **14. LETO** v Sloveniji[1]

Več kot
1.100.000 BOLNIKOV
po svetu se zdravi z zdravilom HUMIRA*[3]

74 KLINIČNIH RAZISKAV
v največji publikaciji o varnosti zaviralcev TNF-α[4]

20 LET KLINIČNIH IZKUŠENJ
z začetki pri revmatoidnem artritisu[4]

15 ODOBRENIH INDIKACIJ
največ med biološkimi zdravili za samoinjiciranje[2]

HUMIRA
Edinstveni temelji za prihodnost

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Humira 40 mg raztopina za injiciranje v napolnjeni injekcijski brizgi I **Humira 40 mg** raztopina za injiciranje v napolnjenem injekcijskem peresniku

Sestava: Ena 0,4 ml napolnjena injekcijska brizga oz. en 0,4 ml napolnjen injekcijski peresnik z enim odmerkom vsebuje 40 mg adalimumaba. Adalimumab je rekombinantno humano monoklonsko protitelo. **Terapevtske indikacije:** Revmatoidni artritis: v kombinaciji z metotreksatom: zdravljenje zmernega do hudega aktivnega revmatoidnega artritisa pri odraslih bolnikih, kadar odziv na imunomodulirajoča zdravila, vključno z metotreksatom, ni zadosten; zdravljenje hudega, aktivnega in progresivnega revmatoidnega artritisa pri odraslih, ki prej še niso dobivali metotreksata. Juvenilni idiopatski artritis: *Poliartikularni juvenilni idiopatski artritis (JIA):* v kombinaciji z metotreksatom za zdravljenje aktivnega poliartikularnega JIA pri bolnikih od 2.leta starosti, ki se ne odzovejo ustrezno na eno ali več imunomodulirajočih antirevmatičnih zdravil. *Artritis, povezan z entezitisom:* za zdravljenje aktivnega artritisa, povezanega z entezitisom pri bolnikih, starih 6 let in več, ki so se neustrezno odzvali ali so intolerantni za običajno zdravljenje. Aksialni spondiloartritis: *Ankilozirajoči spondilitis:* zdravljenje hudega aktivnega ankilozirajočega spondilitisa pri odraslih, ki se na konvencionalno terapijo ne odzovejo ustrezno. *Aksialni spondiloartritis brez radiografskega dokaza za AS:* zdravljenje odraslih s hudim aksialnim spondiloartritisom brez radiografskega dokaza za AS, toda z objektivnimi znaki vnetja s povišanimi CRP in/ali MRI, ki so nezadostno reagirali na ali ne prenašajo nesteroidnih protivnetnih zdravil. Psoriatični artritis: zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih, če odziv na predhodno zdravljenje z imunomodulirajočimi antirevmatiki ni bil ustrezen. Psoriaza: zdravljenje zmerne do hude kronične psoriaze v plakih pri odraslih bolnikih, ki so kandidati za sistemsko zdravljenje. Psoriaza v plakih pri pediatričnih bolnikih: zdravljenje hude psoriaze v plakih pri otrocih in mladostnikih od 4. leta starosti, ki so se neustrezno odzvali na ali niso ustrezni kandidati za topikalno zdravljenje in fototerapije. Hidradenitis suppurativa: zdravljenje aktivne zmerne do hude oblike hidradenitis suppurativa (acne inversa) pri odraslih in mladostnikih, starejših od 12 let, ki se ne odzovejo zadovoljivo na konvencionalno sistemsko zdravljenje. Crohnova bolezen: zdravljenje zmerno do hudo aktivne Crohnove bolezni pri odraslih bolnikih, ki se ne odzovejo na popoln in ustrezen ciklus zdravljenja s kortikosteroidom in/ali imunosupresivom, ali pa takšnega zdravljenja ne prenesejo oz. imajo zanj medicinske kontraindikacije. Crohnova bolezen pri pediatričnih bolnikih: zdravljenje zmerno do hudo aktivne Crohnove bolezni pri pediatričnih bolnikih (od 6.leta starosti), ki se ne odzovejo zadovoljivo na konvencionalno zdravljenje, vključno s primarno prehransko terapijo in kortikosteroidom in/ali imunomodulatorjem, ali pri tistih, ki imajo intoleranco ali kontraindikacije za tako zdravljenje. Ulcerozni kolitis: zdravljenje zmerno do močno aktivnega ulceroznega kolitisa pri odraslih bolnikih, ki se ne odzovejo zadostno na običajno zdravljenje ali takšnega zdravljenja ne prenesejo oz. imajo zanj medicinske kontraindikaci. Uveitis: zdravljenje nenalezljivega intermediarnega, posteriornega uveitisa in panuveitisa pri odraslih bolnikih, ki se niso zadostno odzvali na zdravljenje s kortikosteroidi, pri bolnikih s potrebo po zmanjšani uporabi kortikosteroidov ali pri bolnikih, pri katerih je zdravljenje s kortikosteroidi neprimerno. Uveitis pri pediatričnih bolnikih: zdravljenje kroničnega, neinfekcijskega, anteriornega uveitisa pri bolnikih, starejših od 2 let, ki se niso ustrezno odzvali ali ne prenašajo konvencionalnega zdravljenja, ali pri katerih konvencionalno zdravljenje ni primerno. **Odmerjanje in način uporabe:** Odmerjanje: Zdravljenje mora uvesti in nadzorovati zdravnik specialist, izkušen v diagnosticiranju in zdravljenju bolezni, za katere je zdravilo Humira indicirano. Oftalmologom se svetuje, da se pred začetkom zdravljenja z zdravilom Humira posvetujejo z ustreznim specialistom. Bolniki, ki se naučijo pravilnega postopka injiciranja, si zdravilo Humira lahko injicirajo sami, če zdravnik presodi, da je to primerno, in je zagotovljeno ustrezno medicinsko spremljanje. Med zdravljenjem z zdravilom Humira je treba optimizirati druge sočasne terapije (npr. kortikosteroide in/ali imunomodulacijska zdravila). *Revmatoidni artritis:* odrasli bolnik: 40 mg adalimumaba vsak 2.teden v enkratnem odmerku v subkutani injekciji. Med monoterapijo lahko bolnikom, katerim se zmanjša odziv na zdravilo Humira 40 mg vsak drugi teden, koristi povečanje odmerka adalimumaba na 40 mg vsak teden ali 80 mg vsak drugi teden. *Ankilozirajoči spondilitis, aksialni spondiloartritis brez radiografskega dokaza za AS in psoriatični artritis:* 40 mg adalimumaba v enkratni subkutani injekciji vsak 2.teden. *Psoriaza:* odrasli bolniki: začetni odmerek 80 mg subkutano, ki mu sledi 40 mg subkutano čez en teden in nato 40 mg subkutano vsak 2.teden. Od 16. tedna dalje bolnikom z nezadostnim odzivom na zdravljenje lahko koristi povečanje pogostnosti odmerjanja na 40 mg vsak teden ali 80 mg vsak drugi teden. *Hidradenitis suppurativa:* 160 mg 1. dan, sledi 80 mg 15. dan in nato 29. dan odmerek 40 mg vsak teden ali 80 mg vsak drugi teden. *Crohnova bolezen:* med indukcijo pri odraslih bolnikih z zmerno do hudo aktivno Crohnovo boleznijo 80 mg 0. teden in nato 40 mg 2. teden. Po indukcijskem zdravljenju je priporočeni odmerek 40 mg v subkutani injekciji vsak drugi teden. Bolnikom, katerim se zmanjša odziv na zdravilo Humira 40 mg vsak drugi teden, koristi povečanje odmerka adalimumaba na 40 mg vsak teden ali 80 mg vsak drugi teden. *Ulcerozni kolitis:* med indukcijo pri odraslih bolnikih z zmerno do močno aktivnim ulceroznim kolitisom 160 mg 0. teden in 80 mg 2. teden. Po indukcijskem zdravljenju 40 mg v subkutani injekciji vsak 2.teden. Bolnikom, katerim se zmanjša odziv na zdravilo Humira 40 mg vsak drugi teden, koristi povečanje odmerka adalimumaba na 40 mg vsak teden ali 80 mg vsak drugi teden. Uveitis: začetni odmerek za odrasle bolnike z uveitisom je 80 mg, čemur sledi 40 mg odmerek vsak drugi teden, ki se ga začne dajati en teden po začetnem odmerku. Pediatrična populacija: *Juvenilni idiopatski artritis:* Poliartikularni JIA od 2. leta starosti: priporočeni odmerek pri bolnikih s poliartikularnim juvenilnim idiopatskim artritisom, starih 2 leti in več, temelji na telesni masi: 10 kg do < 30 kg: 20 mg vsak drugi teden; ≥ 30 kg: 40 mg vsak drugi teden. Uporaba pri bolnikih, starih manj kot 2 leti, za to indikacijo ni primerna. *Artritis, povezan z entezitisom:* priporočeni odmerek pri bolnikih z artritisom, povezanim z entezitisom, starih 6 let in več, temelji na telesni masi: 15 kg do < 30 kg: 20 mg vsak drugi teden; ≥ 30 kg: 40 mg vsak drugi teden. *Psoriaza v plakih pri pediatričnih bolnikih:* priporočeni odmerek pri bolnikih s psoriazo v plakih, starih od 4 do 17 let, temelji na telesni masi: 15 kg do < 30 kg: 20 mg začetnemu odmerku sledi odmerek 20 mg vsak drugi teden, z začetkom en teden po začetnem odmerku; ≥ 30 kg: 40 mg začetnemu odmerku sledi odmerek 40 mg vsak drugi teden, z začetkom en teden po začetnem odmerku. Uporaba zdravila Humira pri bolnikih, starih manj kot 4 leta, za to indikacijo ni primerna. *Hidradenitis suppurativa pri mladostnikih (starejših od 12 let, ki tehtajo najmanj 30 kg):* priporočeni odmerek je 80 mg v 0. tednu, ki mu sledi 40 mg vsak drugi teden z začetkom v 1. tednu, v obliki subkutane injekcije. Pri mladostnikih z nezadostnim odzivom je možno razmisliti o povečanju pogostosti odmerjanja na 40 mg vsak teden ali 80 mg vsak drugi teden. Uporaba pri otrocih, mlajših od 12 let, za to indikacijo ni primerna. *Crohnova bolezen pri pediatričnih bolnikih:* priporočeni odmerek pri bolnikih s Crohnovo boleznijo, starih od 6 do 17 let, temelji na telesni masi: < 40 kg: 40 mg 0.teden, ki mu sledi 20 mg 2.teden, vzdrževalni odmerek je 20 mg vsak drugi teden, v primeru, ko je potreben hitrejši odgovor na zdravljenje, z zavedanjem, da je tveganje za pojav neželenih učinkov povečano ob uporabi večjega začetnega odmerka, se lahko uporabi odmerek: 80 mg v 0. tednu in 40 mg v 2. tednu; ≥ 40 kg: 80 mg 0.teden, ki mu sledi 40 mg 2.teden, vzdrževalni odmerek je 40 mg vsak drugi teden, v primeru, ko je potreben hitrejši odgovor na zdravljenje, z zavedanjem, da je tveganje za pojav neželenih učinkov povečano ob uporabi večjega začetnega odmerka, se lahko uporabi odmerek:160 mg v 0. tednu in 80 mg v 2. tednu. Pri bolnikih, ki se ne odzovejo zadostno, se odmerek lahko poveča: < 40 kg: 20 mg vsak teden; ≥ 40 kg: 40 mg vsak teden ali 80 mg vsak drugi teden. Uporaba pri otrocih, starih manj kot 6 let, za to indikacijo ni primerna. *Uveitis pri pediatričnih bolnikih:* priporočeni odmerek pri pediatričnih bolnikih z uveitisom, starih 2 leti ali več, temelji na telesni masi: <30 kg: 20 mg vsak drugi teden v kombinaciji z metotreksatom. Na začetku zdravljenja se lahko uporabi polnilni odmerek 40 mg en teden pred začetkom vzdrževalnega zdravljenja; ≥30 kg: 40 mg vsak drugi teden v kombinaciji z metotreksatom. Na začetku zdravljenja se lahko uporabi polnilni odmerek 80 mg en teden pred začetkom vzdrževalnega zdravljenja. Uporaba pri otrocih, mlajših od 2 let, za to indikacijo ni primerna. *Ulcerozni kolitis pri pediatričnih bolnikih:* Varnost in učinkovitost zdravila Humira pri otrocih, starih 4 – 17 let, ni bila potrjena. Uporaba pri bolnikih, starih manj kot 4 leta, za to indikacijo ni primerna. *Psoriatični artritis in aksialni spondiloartritis, vključno z ankiloznim spondilitisom:* Uporaba pri pediatrični populaciji ni primerna. Način uporabe: uporablja se kot subkutana injekcija. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Aktivna tuberkuloza ali druge hude okužbe in oportunistične okužbe. Zmerno do hudo srčno popuščanje. **Posebna opozorila in previdnostni ukrepi:** Okužbe: Bolniki, ki uporabljajo antagoniste TNF, so bolj dovzetni za resne okužbe. Okvarjena pljučna funkcija lahko zveča tveganje za razvoj okužbe. Bolnike je zato treba pred, med in po zdravljenju natančno kontrolirati glede okužb, vključno s tuberkulozo. Ker lahko eliminacija adalimumaba traja do pet mesecev, je treba bolnike ves ta čas nadzirati. Zdravljenja se ne sme začeti pri bolnikih z aktivnimi okužbami. Bolnike, pri katerih se med zdravljenjem pojavi nova okužba, je treba natančno nadzirati. *Resne okužbe:* Opisane so bile resne okužbe, vključno s sepso, zaradi bakterijskih, mikobakterijskih, invazivnih glivičnih, parazitskih, virusnih in drugih oportunističnih okužb. Med drugimi resnimi okužbami so bile pljučnica, pielonefritis, septični artritis in septikemija. Opisane so bile hospitalizacije in smrti zaradi okužb. *Tuberkuloza:* Poročali so o tuberkulozi, vključno z reaktivacijo in novimi pojavi tuberkuloze. Poročila so vključevala primere pljučne in zunajpljučne tuberkuloze. Pred začetkom zdravljenja je vse bolnike treba pregledati glede aktivne ali neaktivne tuberkulozne okužbe. Če se odkrije aktivna tuberkuloza, se zdravljenja z zdravilom Humira ne sme začeti. *Druge oportunistične okužbe:* Oportunistične okužbe, vključno z invazivnimi glivičnimi okužbami. Reaktivacija hepatitisa B: Reaktivacijo hepatitisa B so opažali pri bolnikih, ki so dobivali antagonist TNF in ki so bili kronični nosilci virusa. Nevrološki zapleti: Antagonisti TNF so bili v redkih primerih povezani s pojavom ali poslabšanjem kliničnih simptomov in/ali rentgenoloških znakov demielinizirajoče bolezni osrednjega živčnega sistema, vključno z multiplo sklerozo in optičnim nevritisom, in periferne demielinizirajoče bolezni, vključno z Guillain-Barré- jevim sindromom. Znana je zveza med intermediarnim uveitisom in demielinizirajočimi boleznimi osrednjega živčevja. Alergijske reakcije: Po uporabi zdravila Humira poročila o resnih alergijskih reakcijah, vključno z anafilaksijo. Imunosupresija: Znakov zavrtja odložene preobčutljivosti, znižanja koncentracije imunoglobulinov ali spremembe števila efektorskih celic T in B, naravnih celic ubijalk, monocitov/makrofagov ali nevtrofilcev niso odkrili. Malignomi in limfoproliferativne bolezni: V kontroliranih delih kliničnih preizkušanj z antagonisti TNF je bilo opaženih več primerov malignomov, vključno z limfomi. Vendar je bilo pojavljanje redko. Med postmarketinškim obdobjem so bili opisani primeri levkemije. Hematološke reakcije: Redko opisana pancitopenija, vključno z aplastično anemijo. Cepljenja: Za pediatrične bolnike je priporočljivo, da pred začetkom zdravljenja z zdravilom Humira opravijo vsa cepljenja v skladu z veljavnimi smernicami za cepljenje, če je le mogoče. Bolniki, ki prejemajo zdravilo Humira, lahko sočasno dobijo cepiva, razen živih cepiv. Uporaba živih cepiv pri dojenčkih, ki so bili izpostavljeni adalimumabu in utero, ni priporočljiva še 5 mesecev po materini zadnji injekciji adalimumaba med nosečnostjo. Kongestivno srčno popuščanje: Pri bolnikih z blagim srčnim popuščanjem potrebna previdnost. Avtoimunska dogajanja: Zdravljenje lahko povzroči nastanek avtoimunskih protiteles. Sočasna uporaba bioloških DMARDS ali antagonistov TNF: Sočasna uporaba z drugimi biološkimi DMARDS (t.j.anakinra in abacept) ali z drugimi antagonisti TNF ni priporočljiva. Operacije: Bolnika, ki med zdravljenjem potrebuje operacijo, je treba natančno nadzirati glede okužb. Zapora tankega črevesa: Če se bolnik ne odzove na zdravljenje Crohnove bolezni, lahko to pomeni, da ima stalno fibrotično strikturo, zaradi katere utegne biti potrebno kirurško zdravljenje. Razpoložljivi podatki kažejo, da zdravilo Humira ne poslabša in ne povzroči striktur. Starejši ljudje: Posebna pozornost glede tveganja okužb. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** V kombinaciji z metotreksatom, je bilo nastajanje protiteles v primerjavi z monoterapijo manjše. Kombinacija zdravila Humira in anakinre ter zdravila Humira in abatacepta ni priporočljiva. Plodnost, nosečnost in dojenje: Adalimumab se med nosečnostjo lahko uporablja samo, če je brez dvoma potrebno. Ženske v rodni dobi morajo premisliti o uporabi ustrezne kontracepcijske zaščite za preprečitev nosečnosti in z njo nadaljevati vsaj še 5 mesecev po zadnjem zdravljenju z zdravilom Humira. Zdravilo Humira se lahko uporablja med dojenjem; učinka na dojene novorojenčke ni pričakovati. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Lahko blag vpliv na sposobnost vožnje in upravljanja s stroji. Lahko se pojavita vrtoglavica in poslabšanje vida. **Neželeni učinki:** *Najpogostejši neželeni učinki* so okužbe (kot je nazofaringitis, okužba zgornjih dihal in sinusitis), reakcije na mestu injiciranja (eritem, srbenje, hemoragija, bolečina ali otekanje), glavobol in mišično-skeletne bolečine. *Drugi pogostejši neželeni učinki:* različne vrste okužb; benigni tumor, karcinom kože; levkopenija, trombocitopenija, levkocitoza; preobčutljivost, alergije; zvišanje lipidov, hipokalemija, hiperurikemija, nenormalni nivo natrija v krvi, hipokalcemija, hiperglikemija, hipofosfotemija, dehidracija; spremembe razpoloženja, anksioznost, nespečnost; glavobol, parestezije, migrena, stisnenje živčnih korenin; motnje vidnega zaznavanja, konjunktivitis, vnetje veke, otekanje oči; vertigo; tahikardija; hipertenzija, zardevanje, hematom; kašelj, astma, dispneja; bolečine v trebuhu, navzeja in bruhanje, gastroinestinalna krvavitev, dispepsija, bolezen gastroezofagealnega refluksa. Sjögrenov sindrom; zvišani jetrni encimi; izpuščaj, poslabšanje ali pojav psoriaze, urtikarija, modrice, dermatitis, oniholiza, čezmerno znojenje, alopecija, srbenje; mišičnoskeletne bolečine, mišični spazmi; hematurija, ledvična okvara; reakcija na mestu injiciranja, bolečina v prsih, edemi, povišana telesna temperatura; koagulacija in motnje krvavenja, prisotnost avtoprotiteles, zvišanje laktat dehidrogenaze v krvi; slabše celjenje. **Način in režim izdajanja:** Predpisovanje in izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Nemčija. **Pomembno opozorilo: Pred predpisovanjem preberite navodila za predpisovanje v celoti navedena v Povzetku glavnih značilnosti zdravila. Datum revizije besedila:** 07/2018.

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3. Interni podatki, AbbVie Inc. 4. Burmester GR et all, Ann Rheum Dis. 2013 Apr;72(4):517-24; *podatki december 2017

AbbVie d.o.o., Dolenjska cesta 242c, Ljubljana
Samo za strokovno javnost Datum priprave informacije: september 2018 SI-HUM-180087

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Belakne

adapalen
1 mg/g gel in krema (30 g)

ZDRAVILO 1. IZBORA ZA ZDRAVLJENJE BLAGIH DO ZMERNIH OBLIK AKEN

Po priporočilu NOVIH evropskih smernic za zdravljenje aken[1]

gel 0,1 %
za mastno kožo

- zdravi akne
- hladi in pomirja

Zdravilo BELAKNE:

- za zdravljenje blagih do zmernih oblik aken
- ima hiter učinek, bolniki ga dobro prenašajo (izboljšana komplianca)
- preprečuje težje oblike bolezni
- preprečuje nastanek brazgotin
- zmanjšuje potrebo po dolgotrajni sistemski terapiji
- priporoča se za vzdrževalno zdravljenje

krema 0,1 %
za suho, občutljivo kožo

- zdravi akne
- neguje in vlaži

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Belakne 1 mg/g gel ali Belakne 1 mg/g krema
Sestava: 1 g gela ali kreme vsebuje 1 mg adapalena. **Indikacije:** Zdravljenje blagih do zmernih aken s pretežno prisotnimi ogrci, papulami in pustulami na obrazu, prsih ali hrbtu. **Odmerjanje:** Zdravilo Belakne se uporablja pri otrocih starejših od 12 let in pri odraslih. Varnost in učinkovitost zdravila Belakne pri otrocih, mlajših od 12 let nista bili dokazani. Zdravilo Belakne je treba nanesti na aknozne spremembe kože enkrat na dan, najbolje po umivanju, zvečer pred spanjem. Tanko plast kreme ali gela je treba z blazinicami prstov nanesti na prizadeta mesta na koži tako, da se izogiba očem in ustnicam. Priporočljivo je, da se oceni izrazitost izboljšanja po 3 mesecih zdravljenja z zdravilom Belakne. Če je potrebno zdravljenje s perkutanimi protibakterijskimi zdravili ali benzoil peroksidom, jih je treba na kožo nanašati zjutraj, zdravilo Belakne pa zvečer. **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. Zdravilo Belakne ne sme priti v stik z očmi, usti, robovi nosu ali mukoznimi membranami. Če zdravilo po nesreči pride v stik z očmi, jih je treba izprati s toplo vodo. Ne sme se aplicirati na poškodovano (ureznine in odrgnine), od sonca opečeno ali ekcematozno kožo niti se ga ne sme uporabljati pri bolnikih s hudimi aknami ali aknami na večjih površinah telesa. Pri bolnikih, ki prejemajo retinoidna zdravila se je treba izogibati depilaciji z voskom. Hkratni uporabi zdravila Belakne in perkutanih keratolitikov ali eksfoliacijskih zdravil se je treba izogibati. Ob sočasni uporabi sredstev za luščenje (peeling), medicinskih ali abrazivnih mil, kozmetičnih izdelkov, ki kožo sušijo, adstringentov ali izdelkov, ki dražijo kožo (dišav, lupino limone ali izdelkov, ki vsebujejo alkohol), se lahko stopnjuje učinek draženja. Izpostavljanje sončni svetlobi ali umetnim UV žarkom (vključno s solariji) je treba med uporabo zdravila Belakne zmanjšati na minimum. Kadar se izpostavljenosti soncu ni moč izogniti, je treba uporabljati zaščitna sredstva in zdravljene predele kože zaščititi z obleko. **Interakcije:** Ni znanih interakcij pri sočasni uporabi zdravila Belakne z drugimi zdravili, ki jih lahko uporabljamo perkutano. Kljub temu pa zdravila Belakne ne smemo uporabljati skupaj z drugimi retinoidi ali zdravili s podobnim načinom delovanja. Izogibati se je treba uporabi zdravila Belakne skupaj z vitaminom A (vključno s prehranskimi dodatki). Adapalen ni fototoksičen in ne povzroča alergije na svetlobo, vendar pa varnost uporabe adapalena med večkratno izpostavljenostjo soncu ali UV sevanju ni bila dokazana. Večji izpostavljenosti soncu ali UV sevanju se je treba izogibati. Ker je absorpcija adapalena skozi kožo majhna, so interakcije s sistemsko uporabljenimi zdravili zelo malo verjetne. **Plodnost, nosečnost in dojenje:** Zdravilo Belakne je kontraindicirano med nosečnostjo ali pri ženskah, ki načrtujejo nosečnost. Zdravilo Belakne lahko uporabljate med dojenjem, vendar se zdravila ne sme nanašati na predel prsnega koša, da ne pride v stik z dojenčkom. Učinkov adapalena na dojenčka ni pričakovati, ker je sistemska izpostavljenost doječe matere zanemarljiva. **Vpliv na sposobnost vožnje in upravljanja strojev:** Ni vpliva. **Neželeni učinki:** Suha koža, draženje kože, občutek toplote na koži, eritem, kontaktni dermatitis, občutek nelagodja na koži, pekoč občutek na koži, srbenje, luščenje kože, očitno poslabšanje aken, bolečina, oteklina, mehurji ali kraste na koži in draženje, rdečina, srbenje ali oteklina očesnih vek. **Vrsta ovojnine in vsebina:** Škatla s tubo po 30 g gela ali 30 g kreme. **Režim izdaje:** Rp **Imetnik dovoljenja za promet z zdravilom:** Belupo, d.o.o., Dvoržakova 6, 1000 Ljubljana. **Datum zadnje revizije besedila:** 21. 8. 2018.

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Samo za strokovno javnost

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Sorel combo

kalcipotriol/betametazon

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.

SKRAJŠANI POVZETEK GLAVNIH 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.

ODMERJANJE IN NAČIN UPORABE: Odmerjanje: Zdravilo Sorel combo mazilo nanašamo na prizadete predele enkrat dnevno. Priporočeno trajanje zdravljenja je 4 tedne. Obstajajo izkušnje pri ponavljajočem se zdravljenju z zdravilom Sorel combo mazilo do 52 tednov. Če je po 4 tednih potrebno nadaljevati zdravljenje ali ga ponovno uvesti, se lahko zdravljenje nadaljuje po zdravniškem pregledu in pod rednim zdravniškim nadzorom. Pri uporabi zdravil, ki vsebujejo kalcipotriol, največji dnevni odmerek ne sme presegati 15 g. Zdravil, ki vsebujejo kalcipotriol, ne smemo uporabljati na površini, večji od 30 odstotkov telesne površine. Posebne skupine bolnikov: *Okvara ledvic in jeter:* Varnost in učinkovitost zdravila Sorel combo mazilo pri bolnikih s hudo ledvično insuficienco ali hudo okvaro jeter nista bili ovrednoteni. *Pediatrična populacija:* Varnost in učinkovitost zdravila Sorel combo mazilo pri otrocih, mlajših od 18 let, nista bili dokazani. Trenutno razpoložljivi podatki za otroke, stare 12 do 17 let, so opisani v poglavjih 4.8 in 5.1 SmPCja, vendar priporočil o odmerjanju ni mogoče dati. *Način uporabe:* Zdravilo Sorel combo mazilo je treba nanesti na prizadeto mesto. Za doseganje optimalnega učinka prhanje ali kopanje takoj po nanosu zdravila Sorel combo mazilo ni priporočljivo.

KONTRAINDIKACIJE: Preobčutljivost za zdravilni učinkovini ali katerokoli pomožno snov. Zdravilo Sorel combo mazilo je kontraindicirano pri eritrodermični, eksfoliativni in pustulozni psoriazi. Ker zdravilo vsebuje kalcipotriol, je kontraindicirano pri bolnikih z znanimi motnjami presnove kalcija. Ker zdravilo vsebuje kortikosteroid, je prav tako kontraindicirano pri naslednjih obolenjih: virusne (npr. herpes ali varicella) lezije kože ter glivične ali bakterijske okužbe, okužbe s paraziti, spremembe na koži zaradi tuberkuloze, perioralni dermatitis, atrofija kože, strije, krhke vene v koži, ihtioza, akne vulgaris, akne rozacea, rozacea, razjede, rane.

POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI: Vpliv na endokrini sistem: zdravilo vsebuje močan steroid skupine III, zato se je treba izogibati sočasni uporabi drugih kortikosteroidov. Lahko se pojavi supresija delovanja skorje nadledvične žleze ali vpliv na nadzor sladkorne bolezni zaradi sistemske absorpcije zdravila tudi med topikalnim zdravljenjem. Uporabi zdravila pod okluzivnim povojem se moramo izogibati. Izogibati se je treba uporabi zdravila na velikih površinah kože, na sluznicah ali v kožnih gubah. Vpliv na presnovo kalcija: ob prekoračitvi največjega dnevnega odmerka se lahko pojavi hiperkalciemija. Spremljajoče okužbe kože: v primeru sekundarne okužbe lezij je treba uporabiti zdravljenje s protimikrobnimi zdravili in v primeru poslabšanja zdravljenje s kortikosteroidi prekiniti. Prekinitev zdravljenja: pri prekinitvi zdravljenja lahko pride do povratnega učinka. Dolgotrajna uporaba: pri dolgotrajni uporabi se poveča tveganje za lokalne in sistemske neželene učinke. Uporaba zdravila pri gutatni psoriazi ni preizkušena. Izkušnje o uporabi tega zdravila na lasišču so omejene. Izkušnje sočasne uporabe fototerapije so omejene. Med zdravljenjem se priporoča omejitev ali opustitev pretiranemu izpostavljanju naravni ali umetni sončni svetlobi.

MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ: študije medsebojnega delovanja med zdravilom Sorel combo in drugimi zdravili niso bile izvedene.

NEŽELENI UČINKI: Pogosti: pruritis in luščenje kože. Občasni: bakterijske, glivične in virusne okužbe kože, folikulitis, atrofija kože, poslabšanje psoriaze, dermatitis, eritem, izpuščaj (eksfoliativni, papularni in pustularni), purpura ali ekhimoze, pekoč občutek na koži, draženje kože, spremembe pigmentacije na mestu nanosa, bolečina na mestu nanosa. Drugi manj pogosti neželeni učinki so navedeni v SmPC.

NAČIN IN REŽIM IZDAJE ZDRAVILA: Rp: Predpisovanje in izdaja zdravila je le na recept. **OPREMA:** Škatla s tubo s 60 g mazila. **IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM:** Lek farmacevtska družba d.d., Verovškova 57, 1526 Ljubljana, Slovenija. **INFORMACIJA PRIPRAVLJENA:** februar 2018 (Ref: 30.12.2017)

Pred predpisovanjem ali izdajanjem zdravila, prosimo, preberite celoten povzetek glavnih značilnosti zdravila, ki je na voljo na www.lek.si/vademekum

SAMO ZA STROKOVNO JAVNOST | Informacija pripravljena: februar 2018 | SI1802776252

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član skupine Sandoz

Sorel combo

kalcipotriol/betametazon

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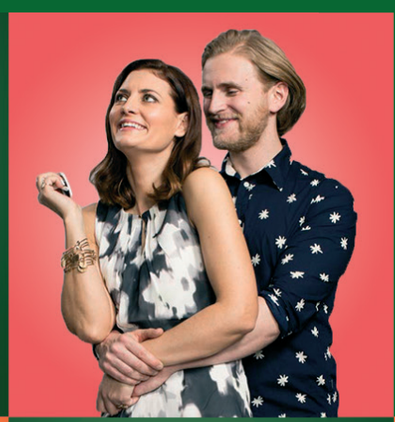

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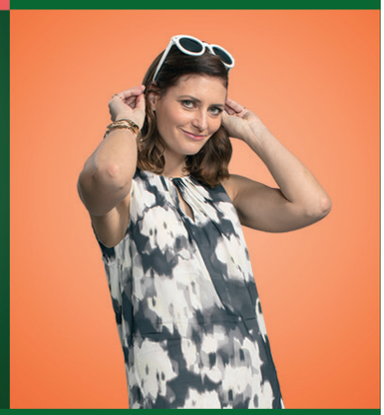

Skrajšani povzetek glavnih značilnosti zdravila Cimzia/certolizumab pegol
Ime zdravila: Cimzia 200 mg raztopina za injiciranje v napolnjeni injekcijski brizgi. **Sestava zdravila:** Ena napolnjena injekcijska brizga vsebuje 200 mg certolizumab pegola v enem mililitru. Certolizumab pegol je fragment Fab' rekombinantnega, humaniziranega protitelesa proti tumorje nekrotizirajočem faktorju alfa (TNFα). Fragment Fab' je pridobljen iz celic *Escherichia coli* ter konjugiran s polietilenglikolom (PEG). **Terapevtske indikacije:** Revmatoidni artritis, aksialni spondiloartritis, psoriatični artritis, psoriaza v plakih **Odmerjanje:** Zdravljenje z zdravilom Cimzia lahko uvede in nadzoruje le zdravnik specialist z izkušnjami v diagnosticiranju in zdravljenju bolezni, za katere je zdravilo Cimzia namenjeno. Bolniki, ki se zdravijo z zdravilom Cimzia, morajo prejeti posebno opozorilno kartico. Polnilni odmerek: Priporočeni 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 z revmatoidnim artritisom in psoriatičnim artritisom med zdravljenjem z zdravilom Cimzia še naprej prejema MTX. Vzdrževalni odmerek: *Revmatoidni artritis:* Po začetnem odmerku je priporočeni vzdrževalni odmerek zdravila Cimzia pri odraslih bolnikih z revmatoidnim artritisom 200 mg vsaka 2 tedna. Ko je klinični odziv potrjen, se lahko uporabi alternativni vzdrževalni odmerek 400 mg vsake 4 tedne. Po potrebi bolnik med zdravljenjem z zdravilom Cimzia še naprej prejema MTX. Aksialni spondiloartritis: Po začetnem odmerku je priporočeni vzdrževalni odmerek zdravila Cimzia pri odraslih bolnikih z aksialnim spondiloartritisom 200 mg vsaka 2 tedna ali 400 mg vsake 4 tedne. *Psoriatični artritis:* Po začetnem odmerku je priporočeni vzdrževalni odmerek zdravila Cimzia pri odraslih bolnikih s psoriatičnim artritisom 200 mg vsaka 2 tedna. Ko je klinični odziv potrjen, se lahko uporabi alternativni vzdrževalni odmerek 400 mg vsake 4 tedne. Po potrebi bolnik med zdravljenjem z zdravilom Cimzia še naprej prejema MTX. Za zgoraj omenjene indikacije kažejo razpoložljivi podatki, da klinični odziv običajno dosežemo v 12 tednih po uvedbi zdravljenja. Pri bolnikih, pri katerih v prvih 12 tednih zdravljenja ni terapevtskega učinka, je treba odločitev o nadaljevanju zdravljenja ponovno skrbno pretehtati. *Psoriaza v plakih:* Po začetnem odmerku je vzdrževalni odmerek zdravila Cimzia za odrasle bolnike s psoriazo v plakih 200 mg vsaka 2 tedna. Pri bolnikih z nezadostnim odzivom se lahko razmisli o odmerku 400 mg vsaka 2 tedna. Razpoložljivi podatki pri odraslih s psoriazo v plakih kažejo, da je klinični odziv običajno dosežen v 16 tednih zdravljenja. Pri bolnikih, ki v prvih 16 tednih ne kažejo znakov terapevtske koristi, je treba dobro razmisliti o nadaljevanju zdravljenja. Pri nekaterih bolnikih z začetnim delnim odzivom se lahko stanje z nadaljevanjem zdravljenja po 16 tednih izboljša. Bolnikom, ki so izpustili odmerek, svetujemo, da si naslednji odmerek zdravila Cimzia vbrizgajo takoj, ko je to mogoče, ter nato z aplikacijo nadaljnjih odmerkov nadaljujejo po osnovnih navodilih. **Način uporabe:** Vsebino cele (1 ml) napolnjene injekcijske brizge je treba aplicirati le v obliki subkutane injekcije. Med ustrezna mesta za injiciranje sodita stegno in trebuh. Z uporabo napolnjene brizge si lahko bolniki zdravilo injicirajo sami, če so bili za to ustrezno usposobljeni ter če zdravnik meni, da je to primerno in bolnikovo zdravljenje po potrebi spremlja. Napolnjeno brizgo z varovalom za iglo lahko uporablja samo zdravstveno osebje. Zdravnik se mora z bolnikom pogovoriti, katera oblika injiciranja je najprimernejša. **Kontraindikacije:** Preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov. Aktivna tuberkuloza ali druge hude okužbe, kot so sepsa ali oportunistične okužbe. Zmerno do hudo srčno popuščanje (razred NYHA III/IV). **Posebna opozorila in previdnostni ukrepi:** v naslednjih primerih: okužbe, tuberkuloza, reaktivacija virusa hepatitisa B (HBV), maligna in limfoproliferativna obolenja, kronična obstruktivna pljučna bolezen (KOPB), kongestivno srčno popuščanje, hematološki pojavi, nevrološki pojavi, preobčutljivost, občutljivost na lateks, imunosupresija, imunizacije, sočasna uporaba drugih bioloških zdravil, operativni posegi, test za določanje aktiviranega delnega tromboplastinskega časa (aPTT), pri starejših bolniki Interakcije: Rezultati populacijske farmakokinetične analize niso pokazali vpliva sočasne uporabe metotreksata, kortikosteroidov, nesteroidnih protivnetnih zdravil (NSAID) in analgetikov na farmakokinetiko certolizumab pegola. Kombinacija certolizumab pegola in anakinre ali abatacepta ni priporočljiva. Sočasna uporaba zdravila Cimzia in metotreksata ni imela pomembnega učinka na farmakokinetiko metotreksata. Primerjava študij je pokazala, da je bila farmakokinetika certolizumab pegola podobna, kot so jo predhodno opazili pri zdravih prostovoljcih. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi: Pri ženskah v rodni dobi je treba razmisliti o uporabi ustrezne kontracepcije. Zaradi hitrosti izločanja zdravila je treba pri ženskah, ki načrtujejo nosečnost, razmisliti o neprekinjeni kontracepciji še 5 mesecev po zadnjem odmerku zdravila Cimzia, vendar je treba upoštevati tudi potrebo po zdravljenju ženske. Nosečnost: Podatki iz več kot 500 prospektivno zbranih nosečnosti, pri katerih so bile ženske izpostavljene zdravilu Cimzia, z znanim izidom nosečnosti, vključno z več kot 400 nosečnostmi, pri katerih so bile ženske izpostavljene v prvem trimesečju, ne kažejo na malformacijski učinek zdravila Cimzia. Vendar so klinične izkušnje, ki so na voljo, preveč omejene, da bi z razumno gotovostjo lahko zaključili, da povečanega tveganja, povezanega z uporabo zdravila Cimzia med nosečnostjo, ni. Uporaba zdravila Cimzia v času nosečnosti lahko zaradi zaviranja TNFα vpliva na normalen imunski odziv pri novorojencu. Zdravilo Cimzia se sme uporabljati med nosečnostjo samo, če je klinično potrebno. V eni klinični študiji je 16 žensk med nosečnostjo prejemalo certolizumab pegol. Koncentracije certolizumab pegola v plazmi, izmerjene pri 14 dojenčkih ob rojstvu, so bile pri 13 vzorcih pod mejo kvantifikacije (BLQ-*Below the Limit of Quantification*); pri enem vzorcu je bila koncentracija 0,042 µg/ml, razmerje koncentracij v plazmi pri materi in dojenčkom ob rojstvu pa je bilo 0,09 %. Po 4 in 8 tednih so bile koncentracije pri vseh dojenčkih pod mejo kvantifikacije. Klinični pomen majhnih koncentracij certolizumab pegola pri dojenčkih ni znan. Dojenje: V klinični študiji pri 17 doječih ženskah, ki so prejemale zdravilo Cimzia, je bilo prehajanje certolizumab pegola iz plazme v materino mleko minimalno. Ocenili so, da je odstotek materinega odmerka certolizumab pegola, ki doseže dojenčka v 24-urnem obdobju, od 0,04 % do 0,30 %. Poleg tega je certolizumab pegol beljakovina, ki se po peroralnem zaužitju razgradi v prebavilih, zato je absolutna biološka uporabnost pri dojenem otroku pričakovano zelo majhna. Posledično se zdravilo Cimzia lahko uporablja med dojenjem. Plodnost: Pri samcih glodalcev so opazili učinke na rezultate meritev gibljivosti spermijev in tendenco zmanjševanja števila spermijev, vendar brez opaznega vpliva na plodnost . V kliničnem preskušanju, v katerem so ocenjevali učinek certolizumab pegola na parametre kakovosti sperme, je 20 zdravih moških naključno prejelo enkratni subkutani odmerek 400 mg certolizumab pegola ali placebo. Med 14-dnevnim spremljanjem ni bilo opaziti učinkov zdravljenja z certolizumab pegolom na parametre kakovosti sperme v primerjavi s placebom. **Povzetek neželenih učinkov:** Pogosti: bakterijske okužbe (vključno z abscesom), virusne okužbe (vključno s herpes zoster, papiloma virusom, gripo), eozinofilija, levkopenija (vključno z nevtropenijo in limfopenijo), glavobol (vključno z migreno), motnje zaznavanja, hipertenzija, navzea, hepatitis (vključno s povečanimi vrednostmi jetrnih encimov), izpuščaj, pireksija, bolečina (na različnih mestih), astenija, pruritus (na različnih mestih), reakcije na mestu injiciranja. **Način in režim predpisovanja ter izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept zdravnika specialista usreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruselj, Belgija. **Pred predpisovanjem, prosimo, preberite Povzetek glavnih značilnosti zdravila. Datum revizije besedila:** 07/2018. **Datum priprave informacije:** 02/2019.

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- Current evidence suggests that nonlesional, or normal-looking, atopic skin is not normal because of persistent subclinical inflammation[1-4]
- 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[1,5]
- This subclinical inflammation throughout the body is a source of lesions and itch, primary signs and symptoms of atopic dermatitis[1,2,4]

DISCOVER THE INFLAMMATION BENEATH

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