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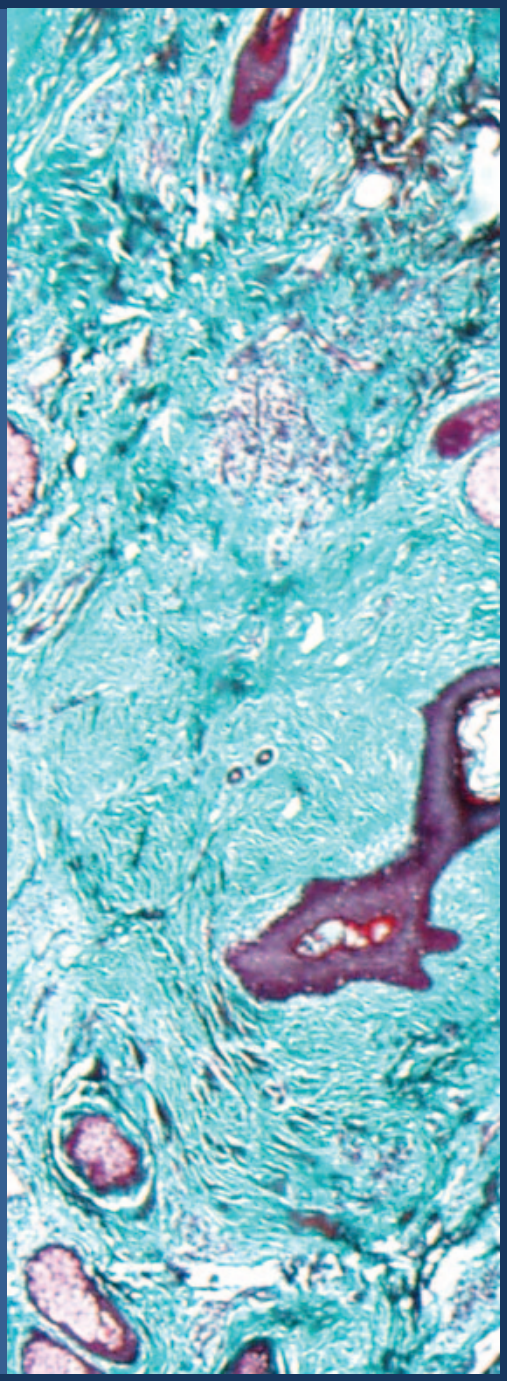

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Evaluation of Efficacy and Safety Profile of Intense Pulsed Light Treatment in Melasma in Darker Skin Type

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Abstract

Introduction. We undertook a prospective, interventional study to evaluate the efficacy and safety profile of Intense Pulsed light (IPL) treatment of melasma in dark skin phenotypes. **Material and Methods.** The study was conducted in 32 patients of skin type IV and V. IPL with 640 nm and 690 nm filters was used. The patients were called once a month to undergo 6 sessions. Melasma area and severity index (MASI) and Clinician Global Impression Scores were used for evaluation. We followed "per protocol" analysis. **Results.** Out of 26 patients who completed the treatment, 12 patients showed improvement, MASI remained unchanged in 10 patients and 4 patients showed deterioration. MASI scores before and after treatment were 6.70 ± 3.53 and 6.32 ± 3.90 (p value=0.6891). Erythema and pain were the common side effects noted. Seventeen out of 32 patients had thyroid disorders. **Conclusion.** IPL should be avoided as a first line therapy in darker skin type. However, it can be used as an adjuvant therapy in some cases after careful deliberations.

Key words: Intense Pulsed Light Therapy; Melanosis; Skin Pigmentation; Hyperpigmentation; Thyroid Diseases; Erythema; Pain; Treatment Outcome

Introduction

Melasma is one of the most common pigmentary disorders seen by dermatologists and often occurs among women with darker complexion (Fitzpatrick skin type IV-VI) (1). It is an acquired pigmentary disorder characterized by symmetrically distributed hyperpigmented macules, which can be confluent or punctate, mostly on the face. Exact pathogenesis is unknown and various factors have been proposed such as sun exposure (2), hormonal factors (3), stress, pollution (4) and drugs.

Treatment of melasma has always been a challenge often resulting in a non response, adverse events and temporary or partial remission. Lasers, including Q switched Nd:YAG, are slowly becoming popular in the treatment of melasma; however, their efficacy and safety remains controversial (5, 6). Some recent studies have suggested that intense pulse light (IPL) may be effective for melasma (7, 8). However, similar studies in darker skin type are very scarce. We have done a prospective, interventional study to evaluate efficacy and safety profile of IPL in melasma in darker skin types.

Material and Methods

The study was conducted at a tertiary care institution after having been granted the permission by the institutional ethical committee. Thirty-two consecutive patients having melasma, who fulfilled the inclusion and exclusion criteria, were included in the study. All patients aged 18 years and above, attending dermatology outpatient department, who were diagnosed with melasma and gave their consent were included in the study. The patients were subjected to IPL treatment after the proper evaluation. Written informed consent was taken from every patient after explaining the treatment procedure and likely repercussions in their vernacular language.

Patients with connective tissue disorders, psoriasis, vitiligo and keloidal tendencies were excluded from the study. Pregnant and

lactating patients were also excluded from the study. Institutional ethical clearance was taken in compliance with the Declaration of Helsinki. IPL with 640 nm & 690 nm cut off filters were used. The patients were called once a month to undergo 6 sessions.

Details of the results and side effects were noted in case record forms. Melasma area and severity index (MASI) scores were noted in every visit. Association of melasma with thyroid disorders was also investigated. The patients were evaluated for thyroid disorders by measuring T3, T4, TSH levels and also by gathering information regarding intake of thyroid supplement for the same disorders.

If 50-100% reduction in MASI Scire was noted, the results were evaluated as good; if MASI reduction was less than 50% results were evaluated as mild, and as poor if there was no redustion of MASI or increase in MASI. Parameters of IPL treatment are presented in **Table 1.**

Statistical Analysis

We followed "per protocol" analysis, whereby only those patients who completed the entire study period (baseline and 5 follow up session) were considered for the final analysis. Melasma area and severity index (MASI) was calculated by considering 4 areas of face-forehead (30%), right malar (30%), left malar (30%) and chin (10%). Other than this area (A), two other factors were considered – darkness (D) and homogeneity (H). MASI was calculated by (D+H) ×A.

Total MASI score:

Forehead 0.3 (D+H) A + right malar 0.3 (D+H) A + left malar 0.3 (D+H) A + chin 0.1 (D+H)A.

For the statistical analysis, p value was calculated using Mann Whitney U test p value of <0.05 was taken as statistically significant.

Results

Of 32 study patients, 25 were female and 7 were male. We followed "per protocol" analysis, whereby only those patients who completed the entire study (6 sessions) were evaluated for the effect of IPL. The age of our patients ranged from 24-56 years, the mean age being 37.9±7.9 years. Young adults in the 20-40 age were most commonly affected (65.6%). All patients belonged to Fitzpatrick skin type IV and V, the phototype IV being the most common, n=19 patients. The presence of thyroid disorders was also evaluated. Out of 32 patients, 17 (53.12%) had thyroid disorder: 16 cases of hypothyroidism and 1 case of hyperthyroidism. Out of these 16 patients, 7 were newly diagnosed, and the others were already on treatment. Of these 17 patients, 2 also had concomitant diabetes. As for the relation between MASI value and the presence of thyroid disorders, there was a mild correlation seen in Spearman's rho (0.119); however, the p value was found to be 0.56.

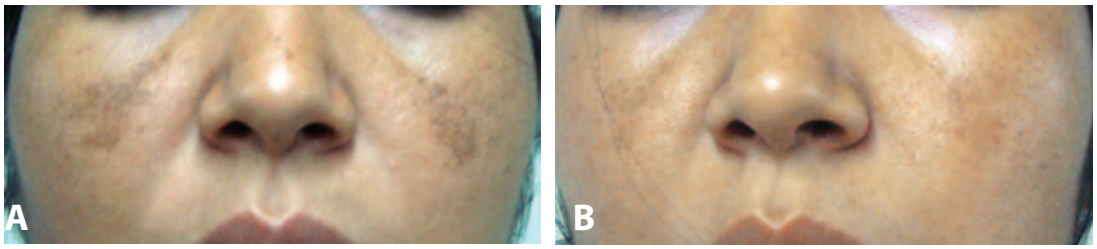
A positive family history of melasma was present in 16 (50%) patients. Based on clinical patterns, we found malar type being predominant as it was seen in 21 (62.13%) patients and most i.e. 30 (93.75%) of them had patchy morphology. On the basis of Wood's lamp

Table 1. IPL parameters

Number of Patients	Filters used	Number of treatments	Interval	Dose
26	640 nm, 690 nm	6	4 weeks	Fluence: 20-30 J/cm^2 (triple pulse) Pulse: 4-6 ms Delay: 20-30 ms

Table 2. Results of the IPL treatment

Number of Patients	MASI score reduction assessment	Clinical global efficacy index
26	Good (50-100% reduction in MASI) - 1 Mild (<50% reduction In MASI) - 11 Poor (no improvement or increase in MASI) - 14	CGI 4 = 0 CGI 3= 1 CGI 2= 11 CGI 1= 14



Figures 1 A and B. (**A)** At beginning of treatment **(B)** Improvement after 6 sessions

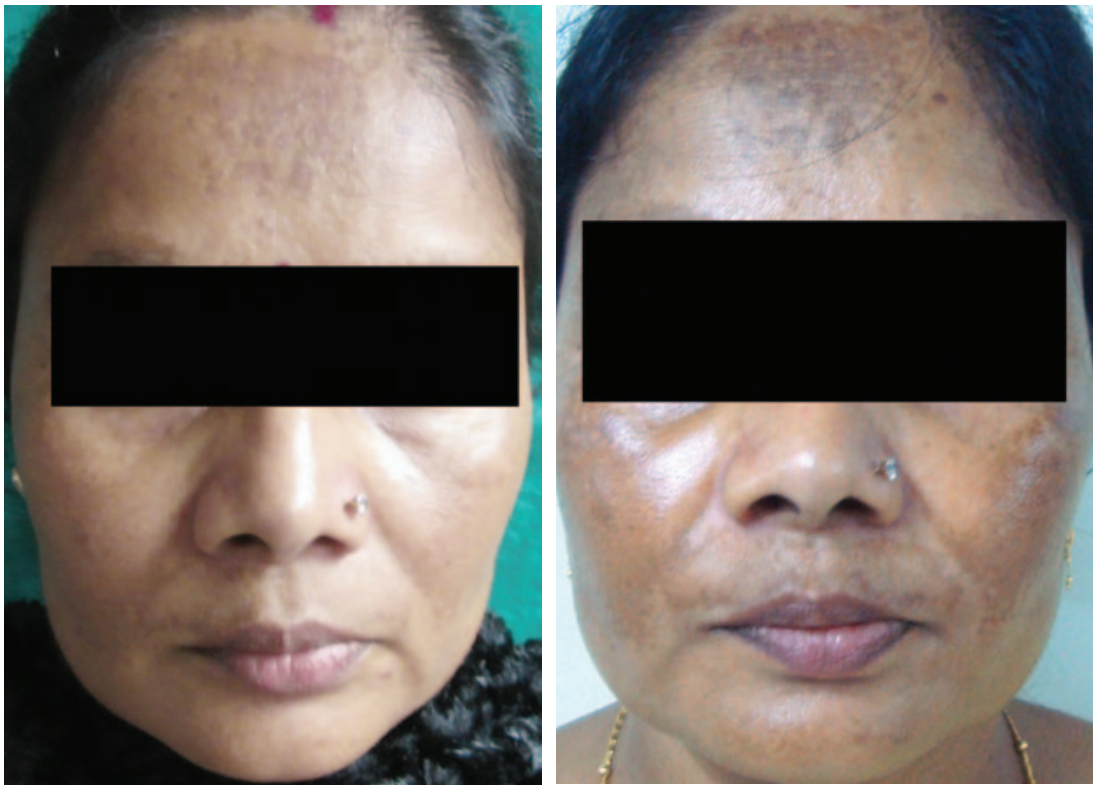
Table 3. Improvement in MASI scores in patients who completed the study (n=26)

	MASI score (baseline) (n=26)	MASI score (end of treatment) (n=26)	P value (in between groups)
Mean ± SD	6.70 ± 3.53	6.32 ± 3.90	
Median (IQR)	5.70(4.8, 7.2)	5.7 (3.6, 7.2)	0.681
Range	2.40-15.60	1.8 – 19.8	

SD=Standard deviation, IQR = Interquartile range, P value between groups by Mann Whitney U test

examination, epidermal type was the predominant type observed in 17 patients, the mixed one was observed in 13 patients and dermal type was found in 1.

Of the 32 patients treated, six patients discontinued treatment due to the development of significant post inflammatory hyperpigmentation (PIH) and were kept out of analysis. Of the 26 patients who completed the



Figures 2 A and B. (**A)** At beginning of treatment **(B)** Increase in MASI following treatment

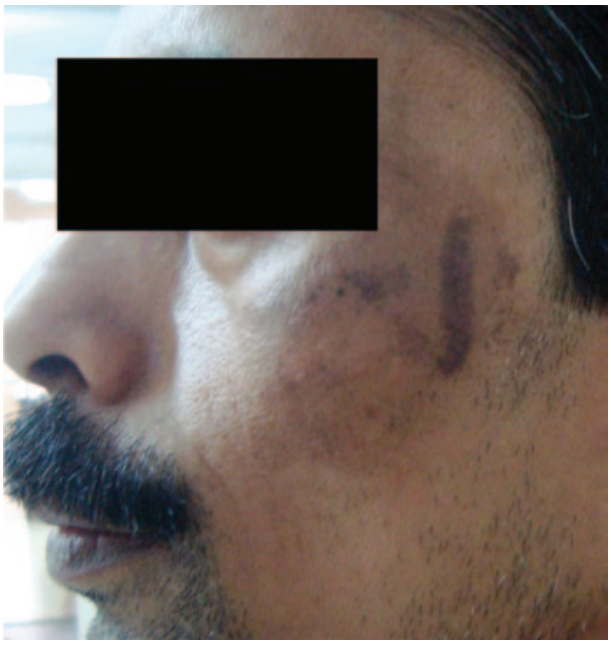


Figure 3. Post inflammatory hyperpigmentation

treatment, 12 patients showed improvement in MASI, **(Figure 1)** whereas MASI remained unchanged in 10 patients and 4 patients showed deterioration **(Figure 2, Table 2)**. The mean MASI score of all the 26 patients taken together before the start of treatment was 6.7±3.53 and after the treatment was 6.32±3.90. However, the improvement was found to be statistically insignificant (p value=0.681) in Mann Whitney tet **(Table 3)**.

When only the patients who had shown improvement were taken, mean MASI of those 12 patients, before and after the treatment was 6.41±3.53 and 4.85±3.90, respectively.

Mild pain, burning sensation and erythema were common side effects noted. No permanent side effects were seen. Treatment was discontinued in 6 patients following post inflammatory hyperpigmentation (PIH) **(Figure 3)**.

We tried to find the predictability of the response against the clinical variable. The response was found to be insignificant for both the clinical types, the malar type (p= 0.681) and the craniofacial type (p=0.643); however, the malar type showed to be correlating better with MASI improvement than the craniofacial type (Spearman's rho value showing moderately strong correlation ρ = -0.245) **(Table 3)**. There was no correlation found between clinical response and baseline MSI score, familiy history and presence of thyroid disorder (p>0.05).

Discussion

Melasma is one of the most common pigmentary disorders and often occurs in persons with darker complexion. It causes significant cosmetic disfigurement which leads to psychological stress as well. There are various modalities of treatment in the form of topical creams and ointments (steroid and hydroquinone containing triple combination cream (9, 10), arbutin (11), kojic acid (12), hydroquinone), oral agents (tranexamic acid) (13, 14) and cosmetic procedures such as chemical peeling (glycolic acid (15), trichloroacetic acid (16) etc.). However, treatments available are found to be either ineffective or partially effective. Many of these treatments have side effects when used for long term.

The invention of lasers and IPL offers a new scope in the treatment of this recalcitrant condition. Various lasers have been tried for treatment of melasma such as QS Nd:YAG (5,1), Erbium YAG (8), QS Ruby (6) and Fractional laser (19). In a Brazilian study involving 302 patients, a high prevalence was found in adult females with skin types III-IV (20). Of the 302 patients, skin type III (34.8%) and skin type IV (384%) were prevailing. In our study 32 patients were recruited and they belonged to Fitzpatrick skin types IV and V. Most of the patients belonged to type IV (59.37%).

In the study conducted by Lutfi et al. in patients with melasma, the frequency of thyroid disorders (58.3%) was 4 times greater than in the control group (21). Estrogen, progesterone, or both could be the triggering factor in the development of melasma in women who have a particular predisposition toward both melasma and thyroid autoimmunity. In our study, thyroid disorders were present in 53.12% of patients. Also a mild correlation was noted between MASI score and the presence of thyroid abnormalities, the correlation coefficient (Spearman's rho) being 0.119.

Wang et al. conducted a study on treatment of melasma using IPL involving 17 patients. The patients underwent four sessions at 4-week intervals (8). The patients were also given 4% hydroquinone cream and broad-spectrum sunscreens. Sixteen patients in the control group were treated with hydroquinone cream and sunscreens. The treatment efficacy was evaluated using reflectance spectrophotometer and patients' satisfaction questionnaire. The patients in the IPL group achieved an average

of 39.8% improvement in relative melanin index, compared to 11.6% improvement in the control group ($p<0.05$) at week 16. More than 50% clearance of lesion was observed in 35%, 26-50% clearance in 35% and < 25% clearance in 30% of patients. Two patients in the intense pulsed light group, however, experienced transient post-inflammatory hyperpigmentation.

A study was conducted by Zoccali et al. in 38 patients to see result of IPL in treatment of melasma (22). In this study 80-100% improvement in lesion was seen in 47.37% (18 patients), 60-79% improvement in 28.95% (11 cases) and moderate improvement (40-59%) in 13.16% of patients (5 cases) and poor in 4 cases (10.52%). They have concluded that IPL stands out as an effective tool in the treatment of melasma, with a very low risk of complications and an excellent satisfaction rate among patients.

In a study conducted by Moreno et al to evaluate the efficacy of IPL in treatment of melasma better results were obtained for epidermal (76-100% clearance) than mixed melasma which showed < 25% clearance of lesion (7). Superficial and deep melanocytic lesions were treated by an intense pulsed light source with thefollowing parameters: filters of 590, 615, and 755 nm, fluence energy of 34-38 J/cm^2, double mode, a pulse width of 3.8-4.5 msec, and a delay of 20 msec, at 4 to 8 week intervals. Two treatment sessions were applied to superficial lesions, while deep ones received four sessions. Side effects were minimal, with no permanent side effects seen.

Our study results were in contrast to those mentioned above. 50-100% improvement was noted in 1 patient, <50% reduction in 11 patients; whereas the remaining 14 showed no improvement or increase in MASI. The inferior response in our patients can be explained by the facts that we have done the study on darker skin types only. In addition we did not use hydroquinone or any other bleaching agent in our patients.

Darker skin types are also more prone to side effects. PIH developed in 6 of our patients; therefore, the treatment was discontinued in those patients. Of these 6 patients, 4 were of Fitzpatrick type V skin and 2 of Fitzpatrick type IV. Thus darker skin appears to be more at risk of developing PIH.

However, in some of our patients (n=12) IPL seems to be working well even without any other bleaching agent; but we did not find any strong correlation between the response pattern and most of the clinical variables In our study, better response was noted in patients with malar type of melasma and in patients with low MASI score.

Conclusion

We suggest that IPL should be avoided as the first line therapy in treatment of melasma especially in darker skin type. However, it can be used as an adjuvant treatment in some patients. We have also concluded that in case of darker skin types, IPL should be used with caution in the treatment of melasma as there is a high chance of post inflammatory hyperpigmentation. We also found that there was association between melasma and hypothyroidism and many of these patients may be unmasked only when investigated for the same.

Abbreviations

IPL – intense pulse light
MASI – Melasma area and severity index
PIH – Post inflammatory hyperpigmentation

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Evaluacija efikasnosti i bezbednosti tretmana melazme intenzivnom pulsirajućom svetlošću na tamnijoj koži

Sažetak

Uvod. Sproveli smo prospektivnu, interventnu studiju da bismo procenili efikasnost i bezbednost intenzivne pulsirajuće svetlosti (IPS) u lečenju melazme kod fototipa IV i V. **Materijal i metode.** Studija je izvedena na 32 pacijenta sa kožom tipa IV i V. Primenjena je intenzivna pulsirajuća svetlost sa filterima 640 nm i 690 nm. Pacijenti su pozivani jednom mesečno na šest seansi. Za evaluaciju su korišćeni indeks površine i intenziteta melazme (*Melasma area and severity index* – MASI i ocena opšteg kliničkog utiska (*Clinician Global Impression Scores*). **Rezultati.** Od 26 pacijenata koji su završili tretman, kod 12 je došlo po poboljšanja, MASI je ostao nepromenjen kod 10 pacijenata, a do pogoršanja je došlo kod četiri pacijenta. MASI vrednosti pre i posle tretmana bile su 6,70 ± 3,53 i 6,32 ± 3,90 (p-vrednost = 0,6891. Eritema i bol su primećeni kao česti prateći efekti. Od 32 pacijenta, 17 su imali tiroidni poremećaj. **Zaključak.** Intenzivnu pulsirajuću svetlost bi trebalo izbegavati kao terapiju prve linije kod tamnije kože. Međutim, može se koristiti kao pomoćna terapija u nekim slučajevima posle pažljivog razmatranja.

Ključne reči: Terapija intenzivnim pulsirajućim svetlom; Melazma; Pigmentacija kože; Hiperpigmentacija; Tiroidne bolesti; Eritem; Bol; Ishod terapije

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Office-made 4% Albendazole Cream is an Effective Alternative Therapy for Cutaneous Larva Migrans: A Report of Three Cases

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Abstract

Introduction. Cutaneous larva migrans (CLM), commonly called creeping eruption, is a parasitic skin disorder caused by the invasion of larva to the skin. This disease classically presents as serpiginous lesions. Larva frequently originates from fecal material of cats and dogs. The pruritus is usually intense and if not treated might disrupt activity, lead to secondary infection, and extend to other regions. Oral and topical antihelminthic agents are the first-line treatment with excellent clinical response. However, they are not always readily available, as is it the case in our region. We attempt to tackle this limitation by formulating an office-made albendazole cream. This report shows the clinical efficacy of our regimen in three cases of CLM. **Case Report.** We report three cases of CLM diagnosed through history taking and clinical presentation. All cases were treated with topical office-made albendazole as requested by the patients and due to resource limitation. The topical preparation was made by dissolving 400 mg albendazole tablet into sterile water and mixing it with Vaseline to form 4% cream. Three times daily application for seven days led to excellent clinical response. **Conclusion.** Our 4% office-made albendazole cream was shown to be effective in treating CLM. Thus, this simple and practical preparation may serve as an alternative treatment for CLM.

Key words: Larva Migrans; Skin Diseases, Parasitic; Antihelmintics; Antiparasitic Agents; Albendazole; Pruritus; Drug Compounding

Introduction

Cutaneous larva migrans (CLM) is a common helminthic dermatosis especially among travellers (1) and those frequently in contact with soil or sand who do not wear adequate foot protection (2-5). The most common infectious agents are *Ancylostomabraziliense* and *Ancylostoma caninum* with typical clinical manifestation of pruritic serpiginous and linear lesions (3, 6). The diagnosis of CLM is established through history taking and clinical presentation. Skin biopsy is rarely needed and reserved for atypical cases (1, 4, 7, 8).

Oral ivermectin and albendazole are the first-line treatment with excellent clinical response (9, 10). However, both are associated with gastrointestinal side effects and allergic reaction (9, 11). Thus, topical treatments, especially in localized lesions, have been advocated since 2016 and are associated with excellent improvement and minimal systemic side effects (3, 6, 12). Topical ivermectin, albendazole, and thiabendazole are commonly used topical treatment (6, 9, 13). Unfortunately, such topical treatments are not always readily available, as is the case in our centre. Topical ivermectin is a costly treatment while topical albendazole and thiabendazole are unavailable in our region. Albendazole is only available in 400 mg tablet but it is often refused by patients who are concerned with the potential side effects. Thus, in order to cope with this limitation, we have attempted to formulate topical Albendazole in multiple occasions which has yielded an excellent clinical response.

Here we report three CLM cases treated by mixing 400 mg albendazole tablet and Vaseline album three times daily with excellent clinical response after five to seven days.

Case Reports

Case 1

A 51-year-old female came with a chief complaint of pruritic and painful erythematous serpinginous lesion on the posterior side of the left leg which had developed a week before admission. The lesion started as an erythematous bump that slowly elevated, elongated, and became increasingly pruritic. The patient denied history of travelling but recalled, as well as contact with cats and dogs. There were cats and dogs around the area. The patient was currently on multiple drugs for heart disease and refused to take another oral drug.

Dermatological examination showed erythematous, slightly elevated serpiginous lesion, crust, pustules, and hyperpigmented macules on the left femoral region **(Figure 1A)**. Larvae were not found under the microscope. The patient was treated with our office-made topical albendazole. Control visit after seven days showed the lesion had resolved leaving hyperpigmented plaque (Figure 1B). Complete resolution was achieved after one month with no relapse until this article was written.

Case 2

A 1.5-year-old boy came with snakelike erythematous lesion on the buttocks and scrotum. The lesions started as an itchy erythematous bump on the buttocks which transformed into snakelike lesion that elongated progressively. The patient often played in his backyard which was full of sand and soil without wearing any clothes. There were cats and dogs around the area.

Dermatological examination showed erythematous, slightly elevated serpiginous lesion with erythematous papule on its end and hyperpigmented macules on the right gluteal region and scrotum **(Figures 2A and 2B)**. No supporting examination was done due to the classical clinical presentation.

Three days after the treatment the patient was reported to stop scratching and the lesion did not further elongate. After seven days, only hyperpigmented macule was left on the gluteus while no lesions remained on the scrotum.

Case 3

A 20-year-old female came with pruritic snakelike erythematous lesion on the upper right arm which had developed five days before admission. Initially the patient complained of an intense itching that turned into erythematous papule and progressed into elevated snakelike linear lesion. There was a history of travelling to the beach in the previous week.

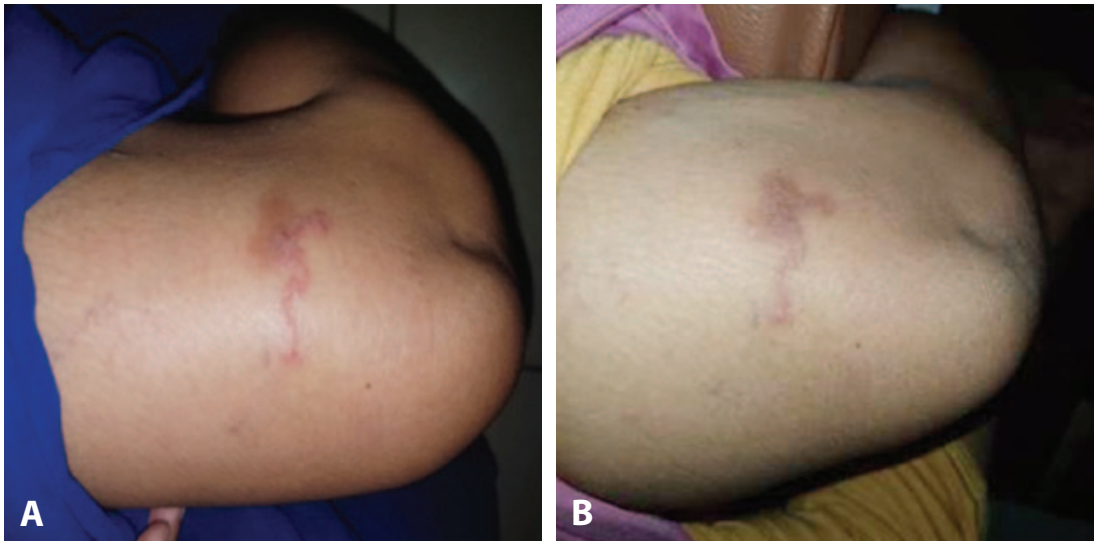

Figure 1. (A) Erythematous, slightly elevated serpiginous lesion, crust, pustules, and hyperpigmented macules on the left femoral region on day 0 (B) After 1 week of treatment, only hyperpigmented macule was left.

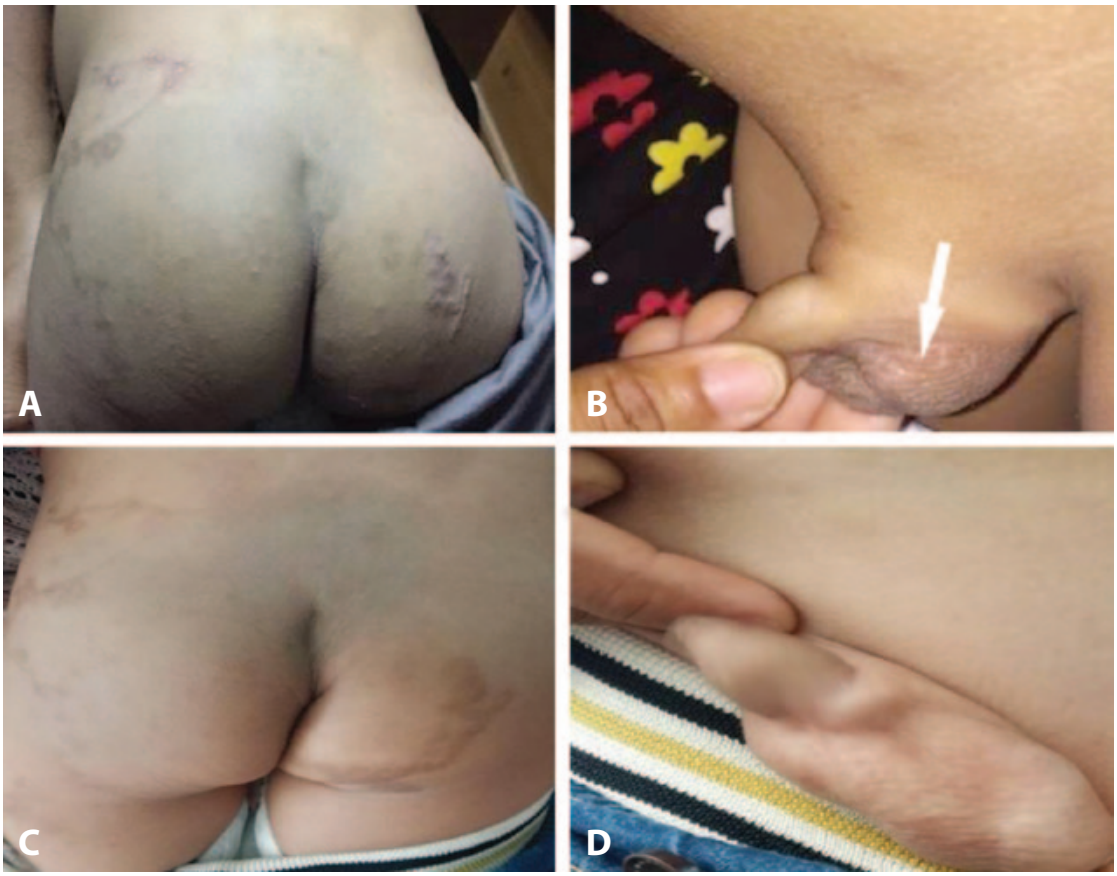

Figure 2. Erythematous, slightly elevated serpiginous lesion with erythematous papule on its end and hyperpigmented macules on the right gluteal region (A) and scrotum (black arrow) (B). Follow-up on day-7 showed hyperpigmented macule on the gluteus (C) and scrotum (D).

Physical examination showed erythematous, partly hyperpigmented, slightly elevated serpiginous lesion with erythematous papule on its end on the right superior extremity **(Figure 3A)**. Skin scraping and microscopic examination did not demonstrate larvae. A diagnosis of CLM was established through history and physical examination.

Figure 3B shows complete resolution of the lesion, leaving only hyperpigmented macule after seven days. Subjectively, the patient reported that the pruritus had ceased after two days of treatment.

All three patients were treated by administering our office-made albendazole cream. Initially, 400 mg albendazole tablet was crushed and dissolved with sterile water. The solution was then mixed with 10 g vaseline album to form 4% cream. In all cases, the cream was applied three times per day.

Discussion

All three patients in our report showed a typical clinical presentation for CLM. Patients with CLM most often seek treatment due to intense pruritus and progressively elongated lesion, with or without complications, as shown in our patients (7, 8). Oral ivermectin and albendazole are the first-line treatment (9, 10). However, oral Ivermectin is not available in our area. Albendazole in 400 mg tablet preparation was available in our center but all patients refused to take oral albendazole. Topical albendazole and thiabendazole were not available in our region while topical ivermectin is very costly and difficult to obtain.

Albendazole shows a potent antiparasitic effect against helminth infection (14). Topical treatment is gradually becoming more popular due to reported side effects of oral preparation (9, 11). Thus, topical application

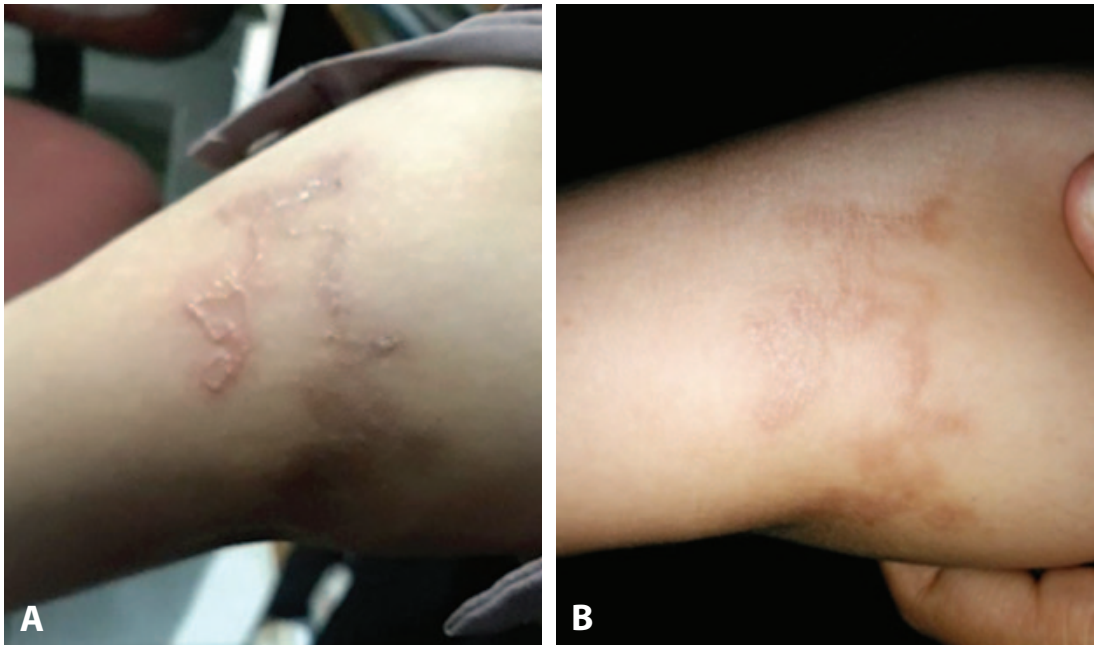

Figure 3. (A) Typical erythematous serpiginous lesionof CLM (B) resolution after seven days of treatment

is expected to result in good clinical response with minimal systemic side effects. Treatment in our three cases included our office-made topical albendazole which was simple and practical. All patients reported excellent clinical response shown by a significant decrease in pruritus and complete resolution of the skin lesion. Albendazole cream was made by crushing 400 mg albendazole tablet and dissolving it in sterile water. The solution was then mixed with 10 g Vaseline album to yield a 4% cream. A similar office-made albendazole cream was mentioned in a previous report with a concentration of 10%. Both cases in the report showed excellent clinical response with no relapse (15). Our report showed that pruritus, which is the main complaint in CLM, was shown to completely resolve after three days. This alternative therapeutic approach is effective in an area with no access to oral or topical anthelminthic agents and in cases where such agents are contraindicated due to risk of systemic side effects (15). This approach has been used in multiple occasions with excellent outcome after three times daily application. No relapse was found after 1-2 months of follow-up.

Conclusion

Our report showed that this office-made 4% albendazole cream applied three times daily for seven days may serve as an alternative therapy with excellent clinical outcome. This is a safe, economic, and readily accessible therapeutic approach for CLM. Larger studies are needed to assess the effectivity of this office-made regimen.

Abbreviations

CLM – Cutaneous larva migrans

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Efikasna alternativna terapija kutane *larve migrans* galenskom 4% albendazol kremom – prikaz tri slučaja

Sažetak

Uvod. Kutana *larva migrans*, poznata kao "puzajuća erupcija", parazitorno je oboljenje kože izazvano invazijom larve na kožu. Ovo oboljenje se klasično manifestuje kao serpiginozne lezije. Larva često potiče iz fekalija mačaka i pasa. Pruritus je obično intenzivan i, ako se ne leči, može ometati svakodnevne aktivnosti, dovesti do sekundarne infekcije i proširiti se na druge regije. Oralni i topikalni antihelminitici su tretmant prve linije i na njih pacijenti dobro reaguju. Mi pokušavamo da rešimo taj problem tako što pravimo galensku albendazol kremu. Ovde prikazujemo efikasnost našeg režima primene kreme na tri slučaja kutane *larve migrans*. **Prikaz slučaja.** Prikazujemo tri slučaja kutane larve migrans, dijagnostikovane na osnovu anamneze i kliničkog pregleda. Svi slučajevi su tretirani topikalnom galenskom albendazol kremom na zahtev pacijenata i zbog ograničenih resursa. Topikalni preparat je pripremljen rastvaranjem 400 mg albendazol tablete u sterilnoj vodi i mešanjem sa vazelinom da bi se dobila 4% krema. Krema je aplicirana tri puta dnevno tokom sedam dana što je dalo dobre rezultate. **Zaključak.** Pokazalo se da je naša galenska 4% albendazol krema efikasna u lečenju kutane larve migrans, i da ovaj jednostavan i praktičan preparat može da posluži kao alternativni tretman kutane *larve migrans*.

Ključne reči: Larva migrans; Parazitske kožne bolesti; Antihelmintici; Antiparazitski lekovi; Albendazol; Pruritus; Priprema farmaceutskih preparata

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Bleomycin-induced Flagellate Dermatitis: a Case Report

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Abstract

Flagellate dermatitis represents a unique cutaneous eruption associated with several causes, including treatment with certain chemotherapeutic agents, ingestion of toxins and rheumatologic conditions like adult-onset Still's disease and dermatomyositis. We present the case of a 35-year-old woman with stage IIA Hodgkin lymphoma who was treated with the ABVD chemotherapy regimen (doxorubicin, bleomycin, vinblastine and dacarbazine). During the third cycle of chemotherapy, she developed multiple linear erythematous macules and hyperpigmentation in a striking flagellate-like pattern localized on the upper chest, submammary folds, neck and upper part of the back. The lesions resolved completely within three months after the withdrawal of bleomycin. Clinicians should be aware of this distinctive cutaneous toxicity in patients receiving bleomycin combination chemotherapy.

Key words: Bleomycin; Drug-Related Side Effects and Adverse Reactions; Erythema; Antineoplastic Combined Chemotherapy Protocols; Hodgkin Disease; Hyperpigmentation

Introduction

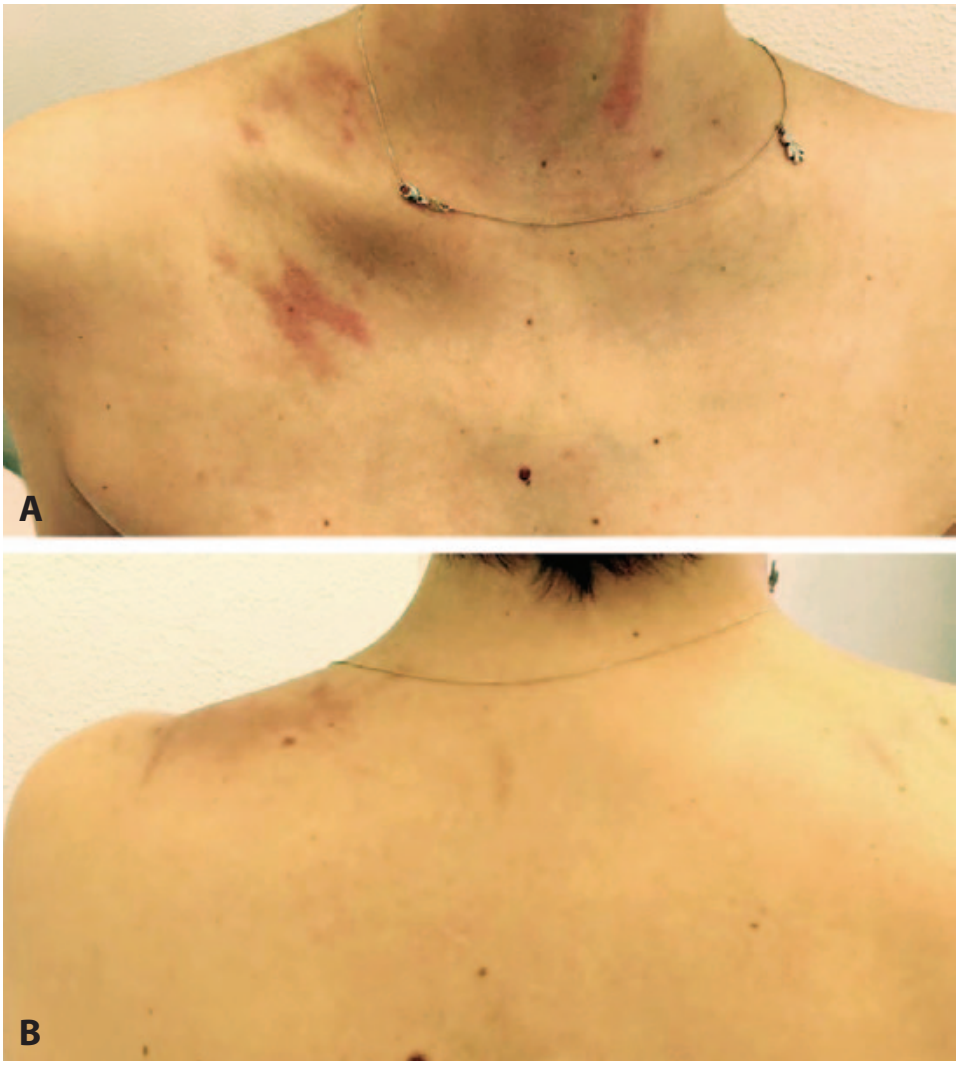
Bleomycin is a cytotoxic chemotherapeutic agent used in the treatment of testicular and ovarian germ cell tumors, lymphomas and squamous cell carcinomas of the head and neck. It is also used for pleurodesis in recurrent malignant pleural effusion, and intralesional bleomycin injections are currently used by dermatologists to treat a number of cutaneous conditions including therapy-resistant verrucae vulgaris, keloids and hypertrophic scars. Beside the well-known pulmonary toxicity, bleomycin is also associated with several mucosal and cutaneous complications. Bleomycin skin toxicity includes flagellate erythema, alopecia, nail bed changes, inflamed nodules on fingers, palmar plantar erythema, eczematous changes, erythematous plaques on knees and elbows, digital gangrene, Raynaud's phenomenon and sclerodermoid lesions (1, 2).

Case report

A 35 year-old Caucasian woman presented to our clinic complaining of a "troublesome" dermatitis of the trunk and neck that had been present for about one month. The patient's medical history was significant for Ann Arbor stage IIA Hodgkin lymphoma of nodular sclerosing subtype, with supraclavicular and extensivemediastinal lymph node involvement. She had no systemic symptoms such as night sweats, weight loss or fever. ABVD chemotherapy regimen (which includes doxorubicin, bleomycin, vinblastine and dacarbazine) was chosen as first-line therapy. The cutaneous lesions appeared during the patient's third cycle of chemotherapy. Routine blood investigations revealed slightly elevated ESR of 27 mm/h while the patient's serologies were negative for HIV and hepatitis B and C viruses.

On physical exam, multiple erythematous-brownish macules with linear distribution were localized on the upper chest, neck and upper part of the back **(Figure 1 A and B)**. A crisscrossing flagellate hyperpigmentation was observed in the submammary folds. All lesions were intensely itchy; there was no evidence of mucosal involvement.

Based on the history and characteristic distribution of the rash, the diagnosis of bleomycin-induced flagellate dermatitis was made. A therapy with high potency topical steroids and oral antihistamines was initiated, which resulted in prompt reduction of the itch but persistence of the skin lesions. Bleomycin was hence later suspended by the hematolo-



Figures 1 A and B. Erythematous-brownish linear streaks in a flagellate-like pattern on the upper part of the trunk and neck

gists and, three months after its discontinuation, complete resolution of the dermatitis was achieved.

Discussion

Flagellate dermatitis (from the Latin *flagellum*) is a cutaneous eruption characterized by erythematous linear streaks in a typical whip-like pattern. Flagellate dermatitis can be caused by a plethora of conditions (3): mechanical causes (i.e. true flagellation because of torture, abuse, religious punishment, sadomasochism, dermatitis artefacta), chemotherapy (due to bleomycin, peplomycin, docetaxel, doxorubicin, cisplatin, trastuzumab, bendamustine), rheumatological diseases (dermatomyositis, adult-onset Still's disease), toxins (shittake mushroom ingestion, *Cnidarian* stings, *Paederus* and other insects), other pruritic dermatoses (dermographism, excoriations in pruritic conditions, phytophotodermatitis, poison ivy dermatitis), human immunodeficiency virus, hypereosinophilic syndrome, Chikungunya fever, or it can be idiopathic. Flagellate dermatitis after bleomycin was first described by Moulin et al. in 1970 as bleomycin-induced linear hyperpigmentation (4). Bleomycin is an antineoplastic antibiotic derived from *Streptomyces verticillus*, first described in Japan by Umezawa in 1966 (5). It acts by generating activated oxygen-free rad-

icals which cause single and double-stranded DNA break and subsequent cell death.

Bleomycin is the most common chemotherapeutic agent to cause flagellate dermatitis, which is observed in 8% to 22% of treated patients (6) and is independent of the route of administration (including after intralesional injection) (7). The skin eruption can first appear 2 hours after the first dose to several weeks after multiple doses (2). While this was previously thought to be dose-dependent, arising in patients with total doses above 100 units,it was later observed after doses as low as 5 units (6). Bleomycin-induced flagellate dermatitis is generally (but now always) preceded by generalized itching (6) and predominantly involves the upper thorax and back. Patch tests with bleomycin are negative, while histological features associated with flagellate dermatitis lack specificity. The most commonly encountered findings include inconspicuous epidermal or spongiotic dermatitis with superficial lymphocytic infiltrates and/or neutrophilic or eosinophilic granulocytes, dermal edema, melanophages in the papillary dermis, epidermal hyperpigmentation (6). In our case, the characteristic morphology of the lesions and the hyperpigmented evolution pointed toward the diagnosis of flagellate dermatitis. Other causes of flagellate dermatitis (e.g. dermatitis factitia) were excluded and, among the drugs our patient had been treated with before developing the skin eruption, bleomycin was the only one associated with flagellate erythema.

Proposed mechanisms which may explain this condition include microtrauma on bony prominence skin areas (6), inflammatory oncotaxis and reduced epidermal turnover – which results in prolonged contact between melanocytes and keratinocytes. It should come as no surprise that bleomycin toxicity involves the skin (along with the lung), sincethe hydrolase which degrades bleomycin is less expressed in the skin and lung compared to other organs, thus resulting intoxic cutaneous concentration of bleomycin (6). Furthermore, scratching may trigger skin vasodilation which also favors local drug accumulation (6). This is consistent with our findings, where the skin lesions were mostly located in skin areas which were accessible to scratching, while the central upper back was relatively spared. Cessation of bleomycin is recommended in severe forms, while systemic antihistamine and steroids (topical or short courses of systemic steroids) may be warranted for symptomatic relief (8). Bleomycin-induced flagellate dermatitis is self-limited and generally recedes within 6 months from the discontinuation of the drug (9). Temporary or, more rarely, permanent hyperpigmentation in the affected area may ensue. Re-exposure to bleomycin is best avoided as it may trigger the recurrence of the skin eruption. The importance of being aware of the existence of this rare cutaneous adverse effect of bleomycin should be underlined because the risk of recurrence is also present for dermatological intralesional use.

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Flagelatni dermatitis izazvan bleomicinom – prikaz slučaja

Sažetak

Flagelatni dermatitis predstavlja jedinstvenu kožnu erupciju povezanu nekolikim uzrocima, uključujući lečenje određenim hemioterapijskim agensima, unošenje toksina i reumatološka stanja poput Stilove bolesti kod odraslih i dermatomiozitisa. Predstavljamo slučaj 35-godišnje žene sa Hočkinovim limfomom IIA stadijuma koja je lečena ABVD režimom hemioterapije (doksorubicin, bleomicin, vinblastin i dakarbazin). Tokom trećeg ciklusa hemioterapije, kod nje su se razvile višestruke linearne eritematozne makule i hiperpigmentacija upečatljivog oblika nalik na tragove biča, lokalizovane na gornjem delu grudnog koša, u podmamarnim naborima, na vratu i gornjem delu leđa. Lezije su u potpunosti nestale u periodu od tri meseca nakon prekida terapije bleomicinom. Kliničari bi trebalo da obrate pažnju na ovu karakterističnu kožnu toksičnost kod pacijenata tretiranih kombinovanom hemioterapijom koja uključuje bleomicin.

Ključne reči: Bleomicin; Neželjena dejstva i reakcije izazvane lekovima; Eritem; Antineoplastični protokoli kombinovane hemoterapije; Hočkinova bolest; Hiperpigmentacija

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A case of Giant Perifollicular Fibroma - a Diagnostic Challenge

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Abstract

Perifollicular fibroma (PFF) is a rare proliferative lesion originating from the perifollicular connective tissue sheath. It may be congenital or acquired manifesting as skin colored to pink, asymptomatic papules of 1-5 mm in size. They are commonly distributed in the head and neck region. Multiple PFFs may be associated with internal malignancy or as a part of Birt-Hogg-Dube syndrome. Histopathology serves as an essential tool in clinching the diagnosis. Herein we report a case of giant congenital PFF.

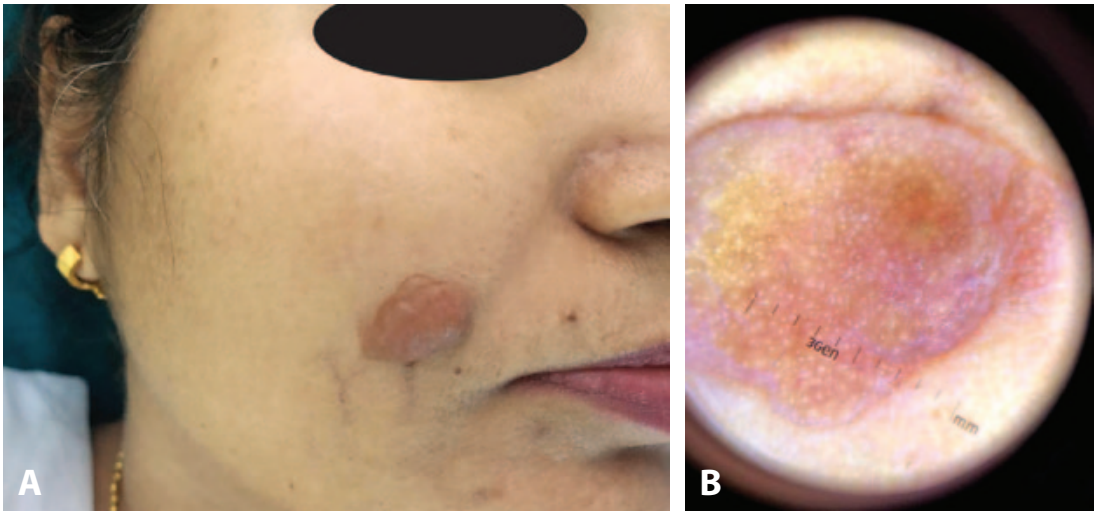
Key words: Fibroma; Hair Follicle; Skin Diseases; Facial Neoplasms; Diagnosis; Hamartoma; Dermoscopy; Case Reports

Introduction

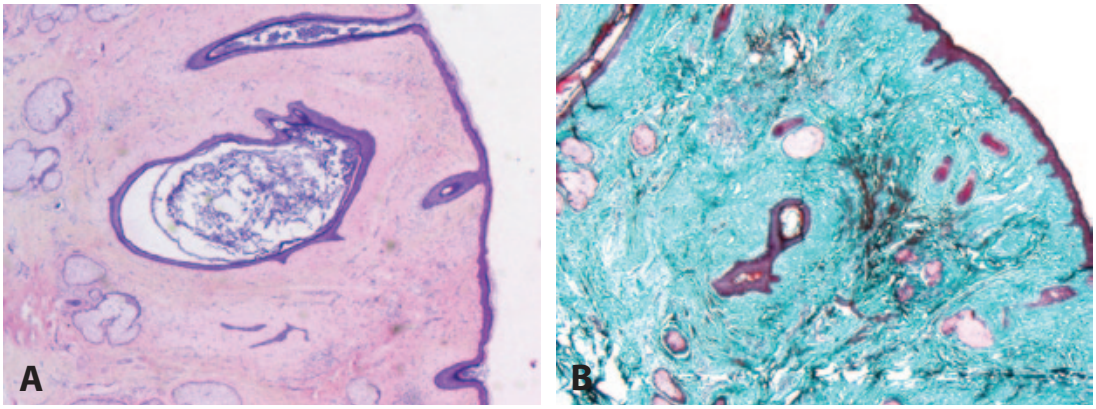
Perifollicular fibroma (PFF) is an uncommon cutaneous hamartoma arising from the connective tissue sheath surrounding the hair follicles. It characteristically presents as solitary or multiple skin colored, dome shaped papules measuring 1-5 mm in diameter. It is usually distributed in the head and neck area. Multiple PFFs are usually associated with colonic polyps and internal malignancy. The etiology of PFF is still doubtful with few studies suggesting them to be neoplastic in nature and few proposing its inflammatory origin (1, 2). Histopathology is crucial in confirming the diagnosis and differentiating it from other conditions. Herein we report a case of giant congenital PFF with characteristic histopathology features.

Case Report

A 49-year old female presented with the complaints of an asymptomatic lesion on the right cheek being there since her birth. The



Figures 1 A and B. (**A)** Clinical picture - A solitary reddish brown, firm, well-defined plaque on the right cheek. **(B)** Dermoscopy showing multiple follicular openings with areas of pallor



Figures 2 A and B. (A) Histopathological section showing follicular plugging with perifollicular concentrically arranged collagen bundles (H & E, 100X). **(B)** Masson's Trichrome staining highlighting perifollicular collagen bundles (100X)

lesion progressively increased in size over the initial few years of life and then stopped progressing further. Her past medical history and family history were unremarkable. Physical examination revealed a solitary, reddish brown, firm plaque on the right cheek just above the nasolabial fold. It was non-tender, 9 mm x 6 mm in size, and on close inspection it showed dilated blood vessels on its surface. **(Figure 1a)**. Dermoscopic examination revealed central area of pallor with numerous follicular openings **(Figure 1b)**.

The lesion was subjected to excisional biopsy which revealed keratinized thinned out epidermis with follicular plugging. Dermis showed collagen bundles arranged concentrically around normal looking hair follicles along with few scattered thinned out blood vessels. A focal lymphocytic infiltrate was also observed. Masson's Trichrome staining was done to highlight the perifollicular collagen bundles **(Figures 2a, 2b)**. However, the staining for elastic tissue was negative. Thus, it was diagnosed as a case of perifollicular fibroma.

Discussion

PFF is a rare cutaneous hamartoma arising from the perifollicular connective tissue sheath. It was first described by Burnier and Rejsek in 1925. They may be congenital or acquired in nature, presenting as asymptomatic, solitary or multiple skin colored to pink, firm papules measuring 1-5 mm in diameter. PFF s are commonly found to be distributed in the head and neck region (1). Multiple PFFs are seen to be associated with colonic polyps, internal malignancy, and bronchiectasis (2). PFF may also occur in association with other benign tumors such as fibrofolliculoma, trichodiscoma and acrochordon as a part of Birt-Hogg-Dube syndrome, which is an autosomal dominant condition (3). The etiopathogenesis of PFF is still unclear with few studies suggesting it to be neoplastic in nature while others reporting it to be an exaggerated fibroblastic response to unknown inflammatory triggers (1, 2).

On histopathology, PFF exhibits concentric layers of ribbon-like collagen bundles around a normal hair follicle giving an onion skin appearance. There is an artifactual cleft that is observed separating the fibroma from the adjacent connective tissue (2). However, the histopathological changes are not seen uniformly across all hair follicles; hence, serial sectioning is important in clinching the diagnosis (4). The common differentials for PFF are fibrofolliculoma, trichodiscoma, dermatofibroma and neurofibroma (1). Though PFF, fibrofolliculoma and trichodiscoma are clinico-pathologically distinct entities, few authors have proposed to consider them as a part of a common spectrum. Fibrofolliculoma is known to show epithelial component in the form of thin anastomosing strands surrounded by a prominent mesenchymalstroma. Trichodiscoma, on the other hand, has a less prominent epithelial component with a marked myxofibrovascularstroma (5). Few authors believe PFF to be a variant of angiofibroma; however, angiofibromas are known to lack concentric perifollicular fibrosis and instead show stellate fibroblasts with increased blood vessels (6).

On immunohistochemistry (IHC), there are CD34 positive spindle cells distributed diffusely and scattered factor XIIIa positive dendritic cells within the connective tissue sheath in PFF (7). In our case, IHC was not done in view of financial constraints. We observed a central area of pallor surrounded by follicular openings on dermoscopic examination; however, we could not establish its significance as there are no reports describing the dermoscopic features of PFF so far.

This case aims to highlight the fact that PFF is a rare condition and the occurrence of a giant solitary PFF as in our case has not been reported so far. It is important for dermatologists to consider PFF as one of the differentials for solitary skin colored papulonodule on the head and neck.

Abbreviations

PFF – Perifollicular fibroma
IHC – immunohistochemistry

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Slučaj gigantskog perifolikularnog fibroma – dijagnostički izazov

Sažetak

Perifolikularni fibrom je retka proliferativna lezija koja nastaje iz omotača perifolukularnog vezivnog tkiva. Može biti urođen ili stečen, a manifestuje se kao koža obojena u roza, asimptomatske papule su veličine od 1 do 5 mm obično se nalaze na glavi i vratu. Višestruki perifolikularni fibromi mogu biti udruženi sa internim malignitetom ili kao deo *Birt-Hogg-Dube* sindroma. Histopotologija je bitna u postavljanju dijagnoze. Ovde prikazujemo slučaj gigantskog urođenog perifolikularnog fibroma.

Ključne reči: Fibrom; Folikul dlake; Kožne bolesti; Neoplazme lica; Dijagnoza; Hamartom; Dermoskopija; Prikazi slučajeva

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DERMOSCOPY OF THE MONTH
Dermatoscopic Features of Combined nevus – a Case Report

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Abstract

Combined nevi (CN), a rare nevus type represent a category of so-called compound tumors. Determined by the presence of two or more different nevus in one biopsy specimen, CN commonly show variable clinical and dermatoscopic features. Therefore, CN could be a diagnostic challenge. We present a 7-year-old Caucasian girl with a pigmented lesion on the arm of no specified duration. Clinical examination showed sharply demarcated pigmented papule. Dermatoscopy revealed a nonchaotic lesion with structureless well defined, minimally eccentric blue area, structureless brown area and brown clods in a symmetric fashion, no vessels and no other clues for melanoma. Histopathology showed a compound common melanocytic nevus, blue nevus in the centre of the lesion with no signs of atypia. Up to now, only 25 cases of CN with dermatoscopic description have been published, withno precise dermatoscopic features established yet. Therefore, studies with larger number of cases are needed for the final conclusions.

Key words: Nevus, Pigmented; Nevus, Blue; Dermoscopy; Child; Case Reports

Introduction

Combined nevi (CN) represent uncommon melanocytic lesions comprised of two or more distinct types of melanocytic nevi (1). Although anymelanocytic nevi could be combined, the most prevalent one is blue nevus associated with common melanocytic nevus (2). Due to various combinations, CN can express variable clinical aspects. As such, CN could be a diagnostic challenge and clinical examination could be insufficient for the correct diagnosis.

Dermatoscopy improves the diagnostic accuracy of melanocytic lesions (3), provides

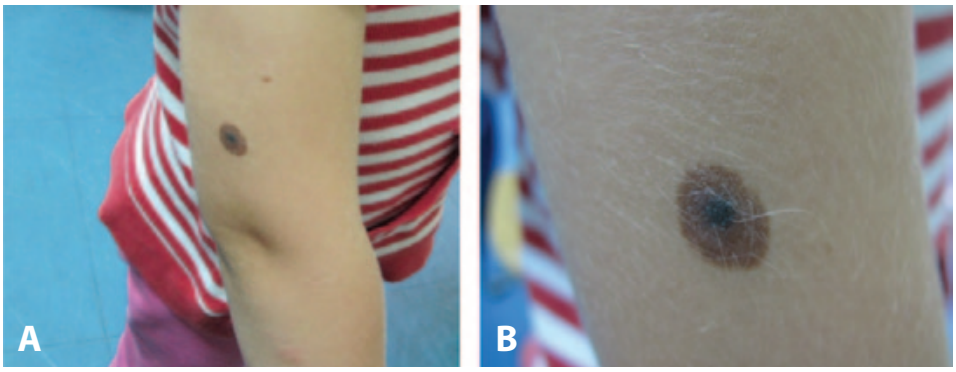

Figure 1. Lesion appearance: A. Pigmented papule on the lateral part of the right arm, B. Close-up of sharply demarcated pigmented papule with a more prominent and pigmented central part.

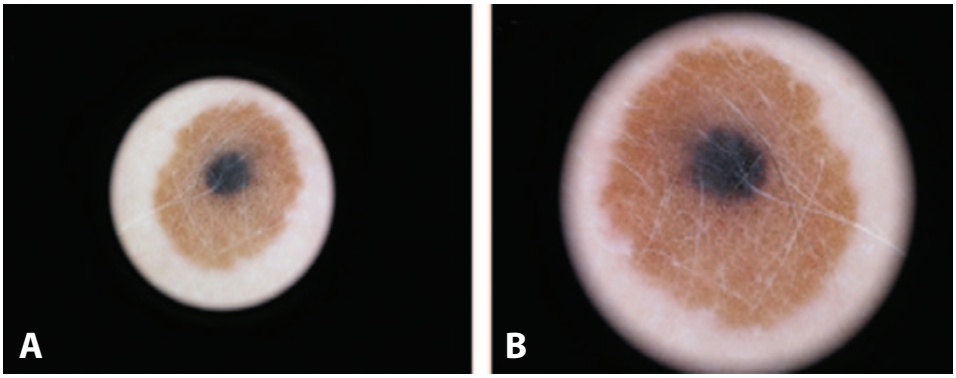

Figure 2. Dermatoscopic features: A. nonchaotic lesion with structureless well defined, minimally eccentric blue area. B. brown structureless, with brown clods in symmetric fashionen circling structureless blue area.

more defining characteristics and increase diagnostic certainty, which can help avoid an unnecessary biopsy. CN represent less than 1% of all biopsied melanocytic nevi (4, 5). Up to now, only 25 cases with dermatoscopic description have been published (6–12), without clearly defined dermatoscopic characteristics of this specific nevi.

Case Report

A 7-year-old Caucasian girl was referred to the Clinic of Dermatovenerology by the surgeon for the dermatoscopic exam of the lesion on her right arm. The history of the lesion was uncertain, and the parents were not sure when exactly the lesion had appeared. The girl was otherwise healthy, did not have any chronic disease and did not receive any medication. The personal and family history for cutaneous malignancies was negative. Clinical examination showed a sharply demarcated pigmented papule with a more prominent and pigmented central part **(Figures 1A, B)**.

The dermatoscopy examination revealed a nonchaotic lesion with structureless well defined, minimally eccentric blue area. The other part of the lesion was mainly brown structureless, with brown clods in symmetric fashion. Vessels were not noted. The dermatoscopic pattern was unusual, but except the eccentric structureless blue area, there were no other specific clues to melanoma **(Figures 2A, B).**

The parents were explained that there were no clues to malignancy based on dermatoscopical examination. Since the dermatoscopic pattern was unusual, the control dermatoscopic exam was advised in 3 months. The parents were not motivated for the control exam, and they insisted having the lesion removed. Excision was performed and the histopathology revealed epidermal and dermal nests of common melanocytic nevus in the majority of the lesion, with no signs of atypia or mitotic activity **(Figure 3A)**. In the center of the lesion slender spindle cells and melanophages were found, corresponding to blue nevus **(Figures 3B, C)**. The diagnosis of a combined nevus was made.

Discussion

Combined nevi are a very rare nevus type (4, 5); they present mostly as a variant of blue nevi, acquired (Clark nevi), congenital (Miescher or Unna nevi) and Spitz nevi (4). They are mainly congenital, although not always visible at birth, but later in life (13). Because of the presence of at least two distinct subtypes of nevi, CN exhibit various appearances on both clinical and dermatoscopic assessment. CN often show unspecific, multicomponent, and peculiar patterns. Therefore, CN can mimic melanomas, their most important differential clinical, dermatoscopical even histopathological diagnosis (4). Larger number of CN have been evaluated only in a few studies, specifying only their clinical and/or histological features (2, 4, 14). Up to now, dermatoscopic features of CN were analyzed only in a small number of cases.

Dermatoscopically, CN appeared as lesions with the simultaneous occurrence of

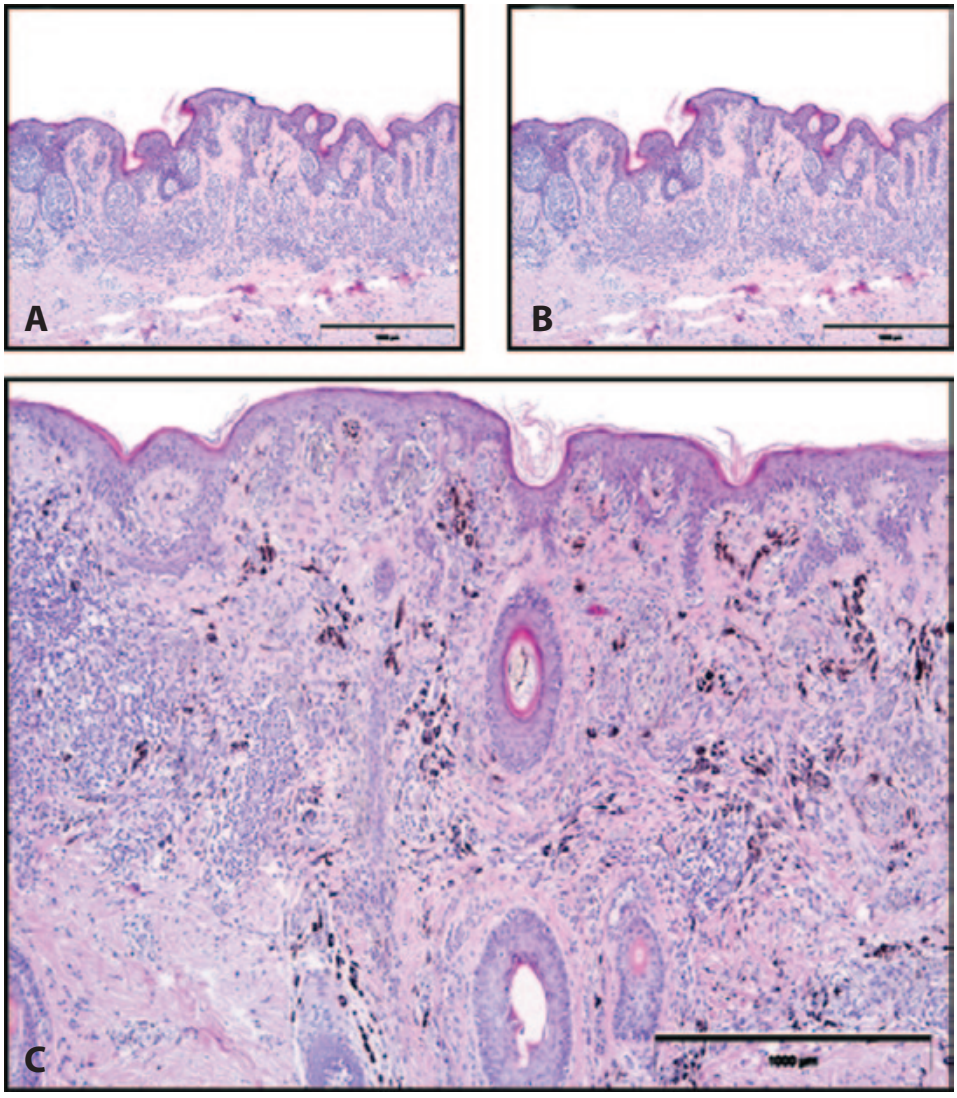

Figure 3. Histopathological findings: **A.** epidermal and dermal nests of common melanocytic nevus, no signs of atypia or mitotic activity: **B, C**. Slender spindle cells and melanophages in the center of the lesion.

different colors, primarily blue and brown, which originates from both junctional and dermal portion of the melanocytes (13). Although CN have multicomponent structure and exhibit at least two patterns, CN commonly show reasonable symmetrical appearance (1). Since chaos (asymmetry of structure or colors) is principally imperative of malignant neoplasm (15), symmetry is one of the most distinguishing features in differentiating CN from melanomas. Therefore, assessing the lesion for chaos first and, if found, proceeding with search for the clues to malignancy is a very useful algorithm for pigmented skin lesion evaluation (13, 15).

Since blue nevus is the most common component of CN, the structureless blue part of the lesion is frequently present and therefore is an important element in the dermatoscopic analysis of CN. Visible structureless blue area is a consequence of histopathological presence of blue nevus (dendritic, cellular blue or deep penetrating nevus) (4) and melanin in the deeper dermal portions. Nevertheless, the presence of ill-defined structureless part of the lesion must always raise suspicion,

since it is a common characteristic of melanomas with the blue part (15). Another characteristic of structureless blue area in CN that needs to be assessed in the dermatoscopic analysisis its size and location within the lesion. Although structureless, the blue one can be presented either with eccentric or central distribution, the latter is considered as more typical for benign lesions. Central homogenous or structureless blue area, surrounded by another pattern (globular or reticular) was previously stated as the stereotypical appearance of CN (16). Presence of eccentric structureless blue area, without other clues to malignancy including grey structures, pseudopods-radial lines, white lines, thick reticular lines, ulcerations, and polygons, could be a significant lead to diagnosis of CN. CN with multicomponent pattern and eccentric structureless blue area, lacking specific dermatoscopic features of melanoma do not require further observation. In dermatoscopic assessment of CN, additional clues that have to be assessed for the correct diagnosis are brown dots and clods, blue/gray dots and clods, curved, reticular or branched lines, as well as radial segmental lines and structureless areas of other colours than blue. Structureless brown could be frequently noticed in CN (6). However, it cannot be considered as a dermatoscopic clue for CN and useful in distinguishing from melanomas with similar aspects, since it could be frequently found in melanomas as well (17). Nevertheless, the presence of structureless white and black ones are another feature specific for melanoma, that directly favours its diagnosis (17).

In dermatoscopic assessment of pigmented lesions, blood vessels morphology is of secondary importance (13). Although blood vessels cannot be used as a clue for pigmented lesions, it could be helpful in further differentiation between CN and melanomas. The prevalence and arrangement of vessels within the lesion could be important to differentiate between the benign and malignant lesion. In CN as benign lesions, the vessels, if present, should demonstrate monomorphic arrangement.

Up to now, the exact dermatoscopic criteria of this particular nevus type have not been established and further studies with a greater number of cases are needed for the final conclusions.

Abbreviations

CN – Combined nevi

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Dermatoskopske karakteristike kombinovanog nevusa – prikaz slučaja

Sažetak

Kombinovani nevusi, retka grupa nevusa, predstavlja vrstu tzv. složenih tumora. Zbog prisustva dva ili više nevusa u jednom bioptiranom uzorku, kombinovani nevusi uglavnom imaju različite kliničke i dermatoskopske karakteristike, te su često dijagnostički izazov. Predstavljamo sedmogodišnju devojčicu bele puti sa pigmentiranom lezijom, bez preciznog vremena nastanka. Kliničkim pregledom uočena je jasno ograničena pigmentna papula na ruci. Dermatoskopija je pokazala nehaotičnu leziju, sa dobro definisanom, minimalno ekcentričnom plavom zonom bez jasne strukture, smeđom zonom bez jasne strukture i simetrično raspoređenim smeđim globulama, bez krvnih sudova i bez karakteristika melanoma. Histopatološkim pregledom je utvrđen složeni melanocitni nevus, sa plavim nevusom centralno, bez znakova atipije. Do sada je objavljeno 25 slučajeva kombinovanih nevusa sa dermatoskopskim opisom, ali bez jasno utvrđenih dermatoskopskih karakteristika ovog tipa nevusa. Neophodne su studije sa većim brojem slučajeva radi konačnih zaključaka.

Ključne reči: Pigmentni nevus; Plavi nevus; Dermoskopija; Dete; Prikazi slučajeva

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AUTHOR GUIDELINES

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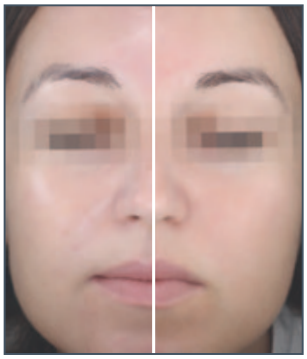

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