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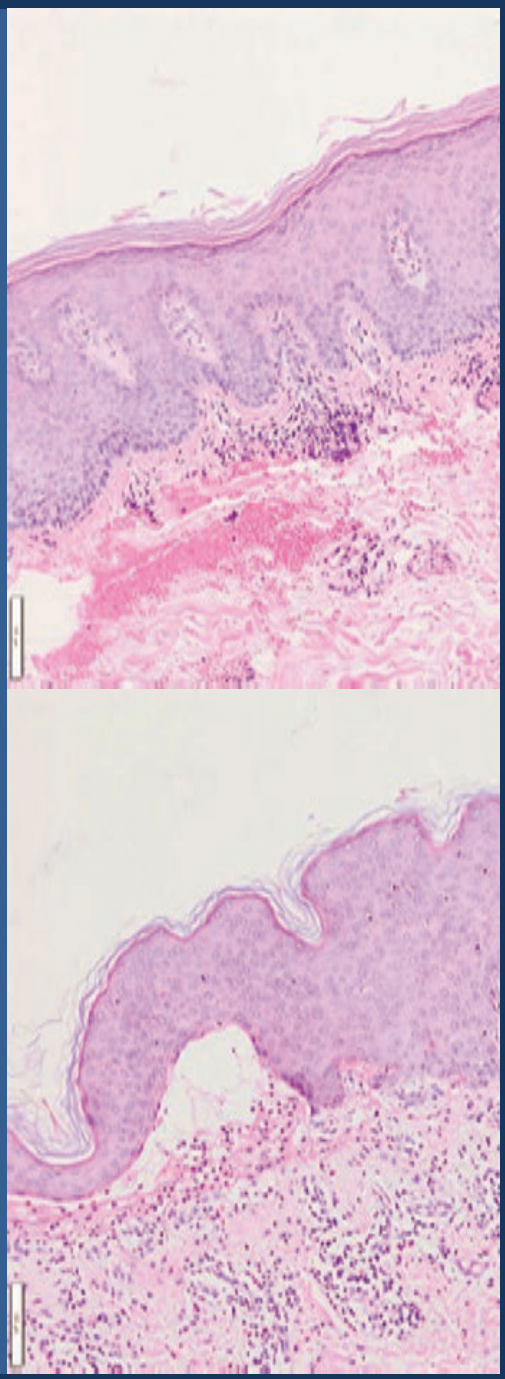

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Rosmarinus Improved Skin Flap Survival Through mTOR Dependent Pathway

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Abstract

Introduction: Skin flap application in the clinical practice is restricted due to the ischemic damage and flap necrosis. Rosmarinus oil has been shown to improve a skin flap survival. In the present work we studied the role of mammalian target of rapamycin (mTOR) signaling on rosmarinus-induced flap protection. **Methods:** A flap surgery was performed on Sprauge-Dawley rats (8 cm in by 3 cm). A week before and a week after the surgery the flaps were treated with topical rosmarinus oil (twice per day). Rapamycin (m-TOR inhibitor) was administered 30 minutes before the flap surgery in rosmarinus-treated or not treated groups. A week after the surgery the malondialdehyde (MDA) contents, myeloperoxidase (MPO) and superoxide dismutase (SOD) activities, expression of Bax, Bcl-2, mTOR and p-mTOR were measured in the flap tissue. **Results:** Topical application of the rosmarinus increased the flap survival ($p<0.05$), anti-oxidative enzyme activity (SOD, $p<0.05$) and anti-apoptotic protein Bcl-2 expression. Rosmarinus treatment decreased the flap MDA content, MPO activity, and pro-apoptotic protein Bax expression ($p<0.05$). Rosmarinus topical application did not change mTOR expression and phosphorylation in the flap tissue. Expression of p-mTOR in rosmarinus treated group was suppressed by rapamycin pre-treatment, which also abolished rosmarinus effects on the flap survival ($p<0.05$). **Conclusion:** These data suggested p-mTOR dependent mechanism in rosmarinus-induced flap survival.

Key words: Rosmarinus; Plant Oils; Ischemia; Reperfusion Injury; Surgical Flaps; Rats, Sprague Dawley; Graft Survival; Necrosis; Apoptosis

Introduction

An important option in the treatment of large damages to the skin tissue is the application of the random skin flaps (1). Regardless of their great potentials, skin flap applications are often limited due to the inadequate blood supply that leads to the partial or complete necrosis at distal parts of the flap (2). Ischemic damage to the flap tissue and subsequent necrosis can be augmented by clinical and pharmacological interventions that suppress oxidative tissue damage or increase tissue tolerance against injury (3, 4). There are several chains of molecular and cellular events which cause flap necrosis including the lack of the nutrients and ATP, oxidative stress, and inflammatory responses (5).

Rosemary (Rosmarinus officinalis L.) is a rich source of active antioxidant constituents such as phenolic diterpenes, flavonoids and phenolic acids. Previous studies on rosmarinus have demonstrated a wide range of beneficial properties including antimicrobial, antioxidant, anti-inflammatory, anti-diabetic, and anticancer effects (6). In two recent studies Ince et al., have shown that rosmarinus increases the skin flap survival by its anti-inflammatory, anti-oxidant and vasodilatory effects (7). In the present work we studied the effect of the oral rosmarinus intake for one week be-

fore flap elevation on decreasing apoptosis. In addition, we also evaluated the possible role of the mammalian target of rapamycin (mTOR) on rosmarinus-induced flap survival.

mTOR, as a central cell-growth regulator, integrates growth factor and metabolic signals to regulate cell survival (8). Pharmacological preconditioning of the tissue to increase its tolerance against ischemic injury has been shown to trigger particular patterns of protein expression including AMPK/mTOR pathway (AMP activated protein kinase and mTOR). Previous results have shown that mTOR phosphorylation can decrease ischemia-induced cellular damage. In accordance with the previous evidence, rosmarinus can activate mTOR/S6K and PI3kinase-akt-mTOR pathways to improve wound healing (9).

Material and Methods

Sprauge-Dawley rats (n=40) were divided into 6 groups (n=10). All protocols were approved by the Institutional Animal Care Committee of University accredited by the Ministry of Health and Medical Education. Skin flap surgery was performed by providing two incisions (8 cm) with 3cm distance on the dorsal surface of the rat and connecting them caudally by a third incision. A transparent foil paper of the same dimensions as the flap was placed between the flap and its donor bed. The whole procedure was done under general anaesthesia (50 mg/kg pentobarbital sodium; intraperitoneally). The percentage of the necrotic area was measured by measuring the total flap surface and necrotic area.

Rosmarinus oil (Now® Foods; purchased from Nutrilife Srl, Italy) was applied in a dose

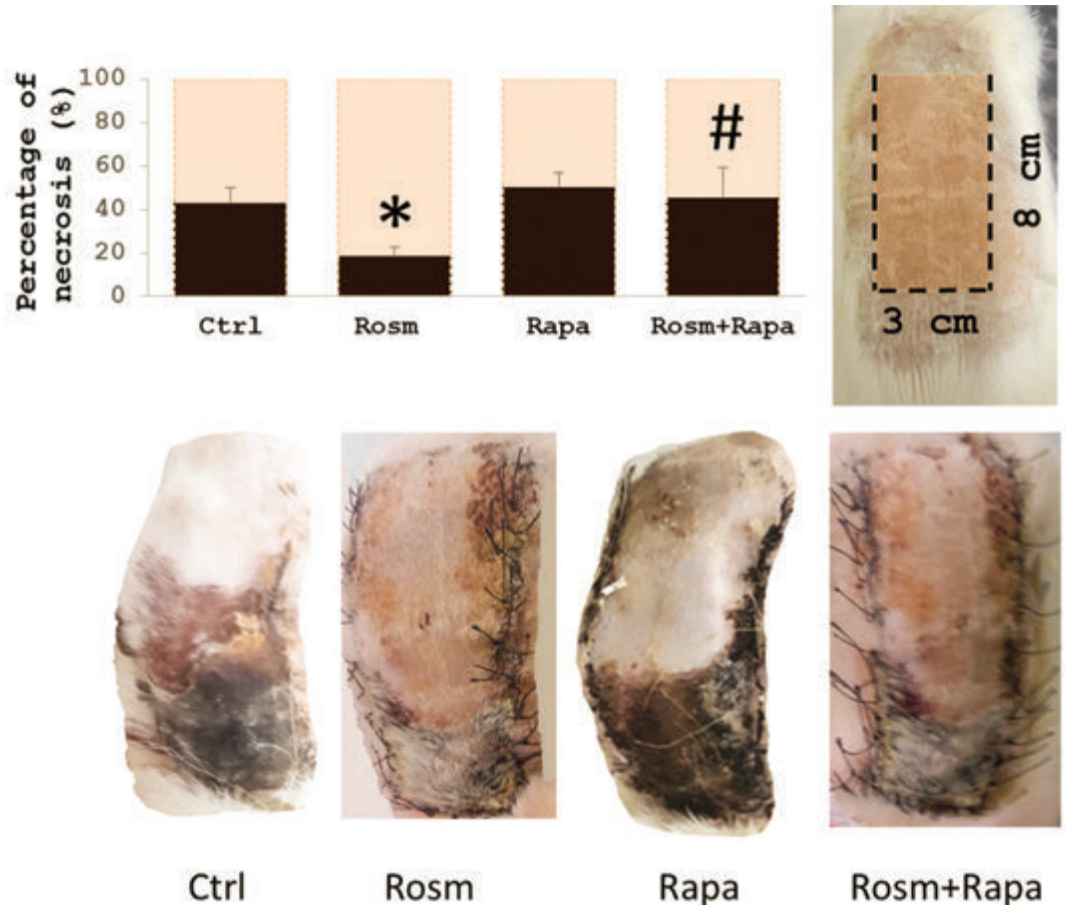

Figure 1. Percentage of the skin flap necrosis in different groups was calculated by dividing necrotic area (black bars) to whole flap area (orange fields). Data are shown as mean ± SDV. *P< 0.05 vs. control group. #p<0.05 when Rosm+Rapa group was compared with Rosmarinus group. Ctrl: control group with flap surgery, Rosm: Rosmarinus, Rapa: rapamycin.

of 0.5 ml per a flap twice a day for one week before and one week after surgery. In two other groups rapamycin (R0395 SIGMA) in a dose of 5 mg/kg was administered intraperitoneally in rosmarinus-treated or non-treated rats 30 minutes before flap surgery. The control group did not receive treatment.

Seven days after flap surgery the necrotic areas were calculated based on the scoring of the length of necrotic area according to the photographs and the percentage of the necrotic area in each flap was calculated. The skin flap samples were collected and preserved for biochemical analysis after sacrificing the animals with an intra-cardiac administration of ketamine (150 mg/kg).

MDA contents and MPO and SOD activities in the flap

The flap tissue was homogenized in 50 mM Tris–ethylenediaminetetraaceticacid (EDTA) buffer (pH 7.0, 4 °C), then centrifuged at 14000×g for 15 min (4 °C). The obtained supernatant was used to determine the levels of MDA contents and MPO and SOD activities. The tissue malondialdehyde (MDA) level, as an index of lipid peroxidation, was determined in homogenized solutions using the Malondialdehyde Assay Kit (Northwest Life Science Specialties, Vancouver, Canada) according to the manufacturer's guide. The superoxide dismutase (SOD) activity was determined using the xanthine oxidase method in accordance to the manufacturer's protocols (Nanjing Jiancheng Biology Institution, Nanjing, China). The MPO activity (Sigma-Aldrich) of the supernatant was determined based on H_2O_2-dependent oxidation of odianizidine 2HCl with spectrophotometer (1unit per minute at 460 nm). The obtained values were expressed as U.mg protein^{-1}.

Bax, Bcl-2, mTOR and p-mTOR expressions in the skin flaps

A bicinchoninic acid protein assay kit (Pierce, Rockford, IL, USA) was used to deter-

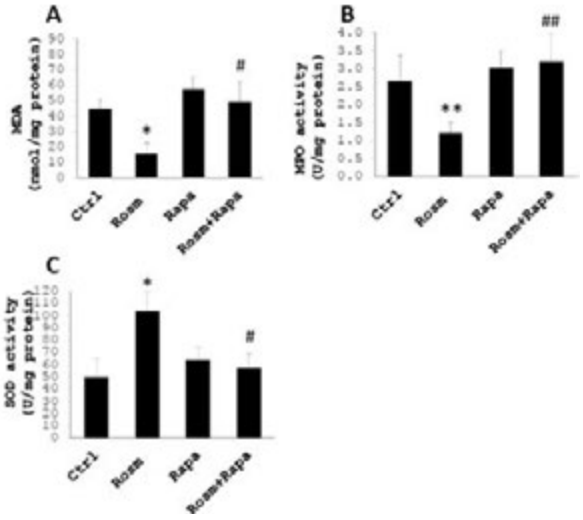

Figure 2. MDA contents and MPO and SOD activities in different groups. A) MDA contents as an index of lipid peroxidation, B) SOD activity as an index of the anti-oxidative activity, and C) MPO activity as an index of the inflammatory reactions. Data are shown as mean ± SDV. *P < 0.05 vs. control group. #p<0.05 when Rosm+Rapa group was compared with Rosmarinus group. Ctrl: control group with flap surgery, Rosm: Rosmarinus, Rapa: rapamycin.

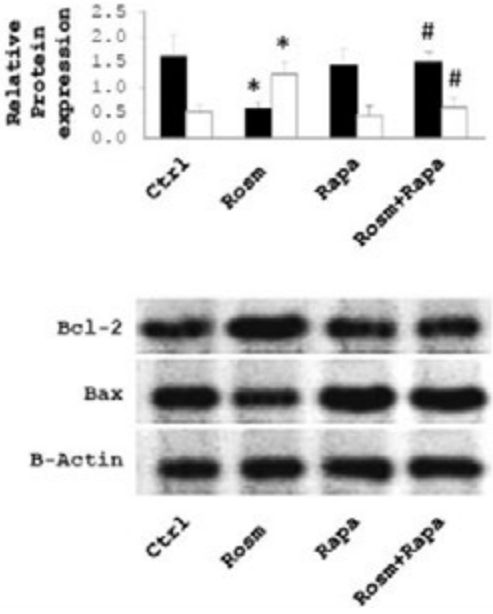

Figure 3. Relative expression of the Bax or Bcl-2 proteins to the β-actin expression in the same sample. Lower panel shows a representative sample from each group. Data are shown as mean±SDV. *P < 0.05 vs. control group. # P < 0.05 when Rosm+Rapa group was compared with Rosmarinus group. Ctrl: control flap surgery, Rosm: Rosmarinus, Rapa: rapamycin.

mine the protein concentrations in the tissue extracts (–80°C). The samples were separated by sodium dodecyl sulphate–polyacrylamide gel electrophoresis on a 7% gel, and incubated for 1.5 h with rabbit polyclonal anti-rat Bcl-2 (ab59348), anti-rat Bax (ab53154), anti-rat b-actin antibodies (ab8227), anti-rat mTOR (ab2732), and anti-phospho-mTOR Ser2481 (Merck, Germany). The membranes were incubated with a horseradish peroxidase-conjugated secondary antibody (rabbit IgG secondary antibody; H&L-Pre-Adsorbed; Abcam), and the protein bands were visualized with an enhanced chemiluminescence system (10).

Statistical analysis

All analyses were performed in SPSS (version 17) and data were presented as Means ± standard deviation. One-way analysis of variance (ANOVA) followed by and Post-Hoc analysis (Tukey test) was used for comparisons between the groups. The level of statistical significance was accepted as $p < 0.05$.

Results

Seven days after flap surgery the percentage of the necrotic area in the non-treated control group was 42.53 ± 7.28 % of the total flap surface. Rosmarinus treatment decreased percentage of the necrotic are to 18.07 ± 4.79 ($p<0.05$; Figure 1). Rapamycin administration before flap surgery did not change necrosis (49.9 ± 6.89). Rapamycin administration in rosmarinus treated group increased the flap necrosis (45.2 ± 13.93 vs. rosmarinus treated group, $p<0.05$; Figure 1).

Skin flap MDA contents and SOD and MPO activities

MDA contents in the skin flap tissue of the control group was 44.01 ± 7.1 nmol/mg protein that was decreased by rosmarinus topical application for one week before surgery and a week after surgery (15.62 ± 6.95, $p<0.05$; Figure 2 A). Rapamycin by itself did not change the MDA contents but it increased the MDA levels in the rosmarinus treated flaps (49.2 ± 13.56, $p<0.05$ vs. the rosmarinus group; Figure 2 A).

The MPO activity, as an index of the neutrophil infiltration, was decreased by the rosmarinus topical application ($p<0.05$ vs. control group; Figure 2 C). This effect was inhibited by rapamycin administration 30 min before surgery ($p<0.05$ vs. rosmarinus group, Figure 2 C). Rapamycin by itself did not change the MPO activity.

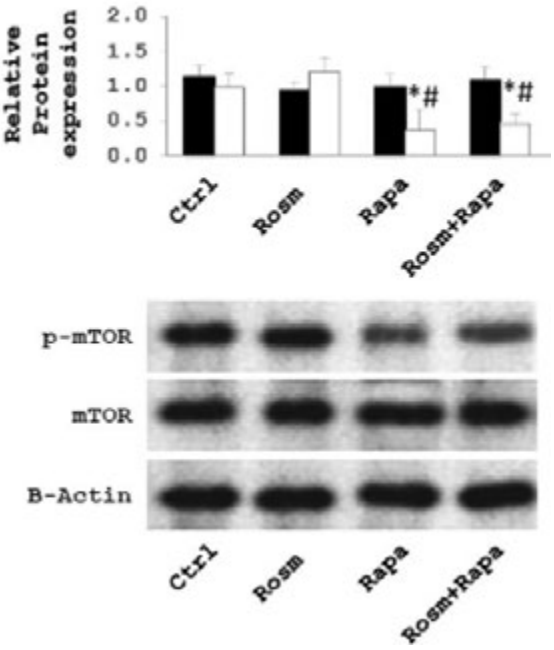

Figure 4. mTOR and p-mTOR proteins expression in the flap tissue. Relative expression of the mTOR or p-mTOR to β-actin was calculated and presented as mean ±SDV. Lower panel shows a representative sample from each group. *P<0.05 vs. control group. # $p < 0.05$ when Rosm+Rapa group was compared with Rosmarinus group. Ctrl: control flap surgery, Rosm: Rosmarinus, Rapa: rapamycin.

The topical application of rosmarinus increased the SOD activity in the flap tissue (103.67 ± 15.66 vs. 49.16 ± 15.56 U/mg protein in the control group, $p<0.05$; Figure 2 B). Pretreatment with rapamycin decreased the SOD activity in the rosmarinus treated groups (56.36 ± 12.82, $p<0.05$; Figure 2 B).

Bax and Bcl-2 expression

The topical application of rosmarinus decreased the expression of the pro-apoptotic protein Bax (0.59 ± 0.12 vs. 1.6 ± 0.42 in the control group, $p<0.05$) and increased the anti-apoptotic protein Bcl-2 expression (1.27 ± 0.23 vs. 0.51 ± 0.14 in the control group, $p<0.01$; Figure 3). Bax and Bcl-2 ex-

pressions did not change by rapamycin administration. However, rapamycin in the rosmarinus treated groups increased Bax expression (1.5 ± 0.19, $p<0.05$ vs. rosmarinus group), and decreased Bcl-2 expression (0.61 ± 0.18, $p<0.05$ vs. the rosmarinus group; Figure 3).

Expression mTOR and phosphorylated mTOR (p-mTOR) in skin flaps

The topical application of rosmarinus for one week before and one week after flap surgery did not change mTOR and p-mTOR expressions in the flap tissue (Figure 4). Rapamycin decreased phosphorylated mTOR (p-mTOR) expression (0.38 ± 0.28 vs. 0.98 ± 0.19 in the control group, $p<0.05$). Rapamycin also decreased p-mTOR expression in the rosmarinus treated flaps (0.46 ± 0.14, $p<0.05$ vs. 1.21 ± 0.2 in rosmarinus group; Figure 4).

Discussion

The rosmarinus topical application for one week before and one week after flap surgery attenuated distal flap necrosis, decreased flap MDA contents, MPO activity, Bax protein expression and increased SOD activity and Bcl-2 protein expression. Anti-necrotic, anti-apoptotic and anti-oxidative effects of the topical rosmarinus are all reversed by blocking mTOR phosphorylation and suggested the involvement of a p-mTOR dependent mechanism in protective effects of rosmarinus.

Several pharmacological agents have been tried to decrease ischemia reperfusion injury in different organs. Protective effects of the rosmarinus topical application, oral administration or intraperitoneal injection on improving the skin flap survival after ischemic injury have been already proved in works by Ince et al. (7). They have shown that rosmarinus treatment increases the blood vessel diameter and therefore the blood supply into the flap tissue. Rosmarinus has also been shown to protect against ischemia reperfusion injury in other organs including the brain, lung and kidney (11). In addition, rosmarinus has been applied on diabetic wounds and radiation-induced tissue damage which confirmed its favorable effects on wound healing (12). In the present work we have shown that rosmarinus suppresses oxidative stress in the flap tissue that is reflected by decreased lipid peroxidation, neutrophil infiltration and increased anti-oxidative enzyme activity.

Previous studies have demonstrated that rosmarinus extract can suppress Hydrogen peroxide (H_2O_2)-induced cellular apoptosis by downregulating Bax and caspase-3 and caspase-9 proteins and upregulation of the Bcl-2 (13). Parallel to its anti-oxidative effects, rosmarinus in the present work decreased apoptotic markers in the flap tissue and prevented from apoptotic cell death. This effect can be related to its vasodilatory effects, which decrease metabolic damage to the mitochondria and therefore decreases the expression of the apoptotic proteins (14).

mTOR integrates different cues, such as oxygen and nutrient levels and energy availability, to regulate cell growth and survival (15). In accordance with the previous study, the increased phosphorylation of mTOR and downstream signaling molecules (S6K1 and 4EBP1) protected the mouse embryonic stem cells (mESCs) against hypoxia-induced apoptosis. An effect that was reversed by mTOR inhibitor rapamycin. It has been shown that rosmarinus treatment can induce mTOR/S6K and PI3kinase-akt-mTOR signaling to improve wound healing (10). In tissue ischemia reperfusion models, mTOR phosphorylation decreased tissue and cellular damage. In the present work rosmarinus treatment did not change the mTOR expression and phosphorylation; however, its protective effect was blocked by suppressing mTOR phosphorylation that suggested mTOR-dependent mechanism for rosmarinus-induced flap survival.

In conclusion, the rosmarinus topical application to the flap tissue decreases necrosis, oxidative damage and apoptosis through mTOR phosphorylation. Even though our data have not shown a direct effect of rosmarinus on mTOR expression and phosphorylation, it seems that mTOR phosphorylation is a key element interacting with signaling pathways involved in the rosmarinus-induced flap survival.

Acknowledgment

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References

1. Lin R, Chen H, Callow D, Li S, Wang L, Li S, et al. Multifaceted effects of astragaloside IV on promotion of random pattern skin flap survival in rats. Am J Transl Res. 2017;9(9):4161-72.
2. Zhou KL, Zhang YH, Lin DS, Tao XY, Xu HZ. Effects of calcitriol on random skin flap survival in rats. Sci Rep. 2016;6:18945.
3. Pazoki-Toroudi HR, Hesami A, Vahidi S, Sahebjam F, Seifi B, Djahanguiri B. The preventive effect of captopril or enalapril on reperfusion injury of the kidney of rats is independent of angiotensin II AT1 receptors. Fundam Clin Pharmacol. 2003;17(5):595-8.
4. Pazoki-Toroudi H, Ajami M, Habibey R, Hajiaboli E, Firooz A. The effect of enalapril on skin flap viability is independent of angiotensin II AT1 receptors. Ann Plast Surg. 2009;62(6):699-702.
5. Peng L, Pan X, Yin G. Natural hirudin increases rat flap viability by anti-inflammation via PARs/p38/NF-kappaB pathway. Biomed Res Int. 2015;2015:597264.
6. González-Vallinas M, Reglero G, Ramírez de Molina A. Rosemary (Rosmarinus officinalis L.) extract as a potential complementary agent in anticancer therapy. Nutr Cancer. 2015;67(8):Ince B, Yildirim AM, Okur MI, Dadaci M, Yoruk E. Effects of Rosmarinus officinalis on the survivability of random-patterned skin flaps: an experimental study. J Plast Surg Hand Surg. 2015;49(2):83-7.
7. Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell. 2006;124(3):471-84.
8. Lou K, Yang M, Duan E, Zhao J, Yu C, Zhang R, et al. Rosmarinic acid stimulates liver regeneration through the mTOR pathway. Phytomedicine. 2016;23(13):1574-82.
9. Pazoki-Toroudi H, Ajami M, Babakoohi S, Khaki L, Habibey R, Akhiani M, et al. Effects of diphencyprone on expression of Bcl-2 protein in patients with alopecia areata. Immunopharmacol Immunotoxicol. 2010;32(3):422-5.
10. Tian XF, Yao JH, Zhang XS, Zheng SS, Guo XH, Wang LM, et al. Protective effect of carnosol on lung injury induced by intestinal ischemia/reperfusion. Surg Today. 2010;40(9):858-65.
11. Abu-Al-Basal MA. Healing potential of Rosmarinus officinalis L. on full-thickness excision cutaneous wounds in alloxan-induced-diabetic BALB/c mice. J Ethnopharmacol. 2010;131(2):443-50.
12. Ghasemzadeh MR, Amin B, Mehri S, Mirnajafi-Zadeh SJ, Hosseinzadeh H. Effect of alcoholic extract of aerial parts of Rosmarinus officinalis L. on pain, inflammation and apoptosis induced by chronic constriction injury (CCI) model of neuropathic pain in rats. J Ethnopharmacol. 2016;194:117-30.
13. Eefting F, Rensing B, Wigman J, Pannekoek WJ, Liu WM, Cramer MJ, et al. Role of apoptosis in reperfusion injury. Cardiovasc Res. 2004;61(3):414-26.
14. Crino PB. The mTOR signalling cascade: paving new roads to cure neurological disease. Nat Rev Neurol. 2016;12(7):379-92.

Ruzmarinom poboljšano preživljavanje režnja kože delovanjem na mehanizme zavisne od mTOR

Sažetak

Uvod. Primena kožnog režnja u kliničkoj praksi je ograničena zbog ishemijskog oštećenja i nekroze režnja. Dokazano je da ulje ruzmarina poboljšava preživljavanje kožnog režnja. U ovom radu proučavali smo ulogu signaliziranja ciljnog molekula za rapamicin kod sisara (*mammalian target of rapamycin* (mTOR)) u zaštiti režnja pomoću ruzmarina. **Metode.** Operacija režnjem je izvedena na *Sprauge-Dawley* pacovima (8 cm sa 3 cm). Nedelju dana pre i nedelju dana posle operacije, režnjevi su tretirani topikalno uljem ruzmarina (dva puta dnevno). Rapamicin (m-TOR inhibitor) je primenjen 30 minuta pre operacije režnjem u grupama koje su tretirane i koje nisu tretirane ruzmarinom. Nedelju dana posle operacije izmeren je sadržaj malondialdehida (MDA), aktivnosti mijeloperoksidaze (MPO) i superoksidaze dismutaze (SOD), ekspresija Bax, Bcl-2, mTOR I p-mTOR u tikvu režnja. **Rezultati.** Topikalna primena ruzmarina povećava preživljavanje režnja ($p < 0,05$), antioksidativnu aktivnost enzima (SOD, $p < 0,05$) i ekspresiju antiapoptotičkog proteina Bax ($p < 0,05$). Tretman ruzmarinom je smanjio sadržaj malondialdehida u režnju, aktivnost mijeloperoksidaze i ekspresiju proapoptotičkog proteina Bax ($p < 0,05$). Topikalna primena ruzmarina nije promenila mTOR ekspresiju i fosforilaciju u tkivu režnja. Ekspresija p-mTOR-a u grupi tretiranoj ruzmarinom je suprimirana prethodnim tretmanom rapamicinom, koji je takođe poništio efekte ruzmarina na preživljavanje režnja ($p < 0,05$). **Zaključak.** Ti podaci su ukazivali na mehanizme zavisne od p-mTOR-a u preživljavanju režnja izazvanom ruzmarinom.

Ključne reči: Ruzmarin; Biljna ulja; Ishemija; Reperfuzione povrede; Hirurški režnjevi; Sprague Dawley pacovi; Preživljavanje grafta; Nekroza; Apoptoza

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Leukemia Cutis – A Case Report

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Abstract

Leukemia cutis is a specific skin lesion which is characterized by diffuse infiltration of neoplastic cells and can occur in all types of leukemia. Leukemia cutis can have varied cutaneous presentations such as papules, macules, nodules, plaques and ulcers. We report a case of 52-year-old woman who presented with erythematous macules and papules over her trunk, thighs and upper arms. A skin punch biopsy showed monomorphic, perivascular and periadnexal infiltration by the cells positive for CD45, CD15, CD68 and lysozyme. According to the subsequent bone marrow biopsy and immunophenotypic analysis of peripheral blood cells, the diagnosis of acute monocytic leukemia (FAB AML-M5b) was made. In our case, the first clinical sign suggestive of the diagnosis of leukemia was the presence of erythematous macules and papules. Therefore, we believe that leukemia cutis should be taken into consideration in the differential diagnosis of maculopapular rush on the trunk, upper arms and leg

Key words: Leukemia, Monocytic, Acute; Skin Neoplasms; Exanthema; Diagnosis, Differential; Case Reports

Introduction

Leukemia cutis is defined as an infiltration of the skin by neoplastic leukocytes causing specific skin lesions (1-3). Specific skin changes include all lesions that are characterized by a leukemic infiltrate and which may be diagnosed as leukemia cutis by histopathology examination, irrespective of the clinical morphology (4). The frequency of leukemia cutis and age distribution of patients suffering from it depend on the leukemia subtype and can occur in all types of leukemia (2). The clinical and morphological findings have a wide range of cutaneous manifestations (papules, macules, nodules, plaques, ulcers) (2, 4-6). In addition, patients with leukemia can develop unspecific skin changes which on biopsy do not contain leukemic cells. These changes are mostly dermatological diseases associated with abnormal hematopoiesis such as thrombocytopenic purpura and opportunistic, often severe infections (generalized herpes zoster, furunculosis, fungal abscess) (2, 4). Here, we report a case of leukemia cutis presenting with a maculopapular eruption disseminated on the trunk, thighs and upper arms.

Case Report

A 52-year-old woman presented to our clinic with a history of low grade fever, and a skin rash, which was present for 2 months. On examination, erythematous macules and papules measuring up to 1 cm were present over her trunk, thighs and upper arms (Figure 1). A punch biopsy of the skin rash was performed. She was diagnosed with pneumonia and hypothyroidism four months before.

At the first presentation, the laboratory results were as follows: red blood cell (RBC) count 3,77 x10^{12}/L, hemoglobin 117 g/L, platelet count 226 $\times$ 10^9/L, total white blood cell (WBC) count 4.62 $\times$ 10^9/L (neutrophil 28.5%, large unstained cells - LUC 25%). The peripheral blood smear showed 22% neutrophils and 27% monocytoid cells, some with lobulated nuclei. Urea, creatinine and transaminases were within normal range. A skin punch biopsy showed monomorphic, perivascular

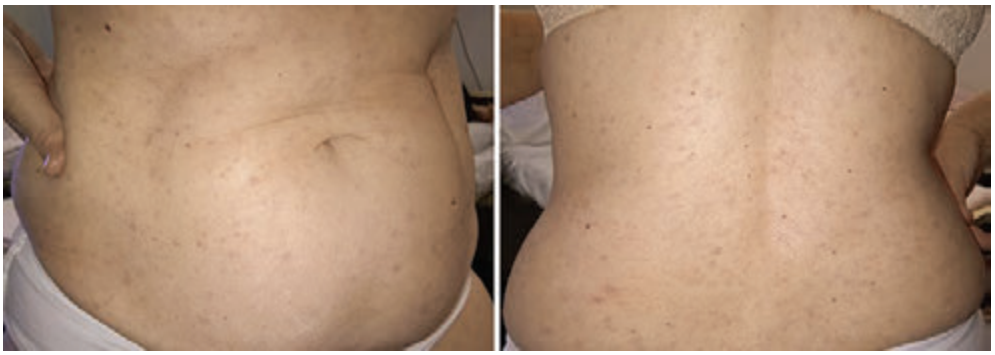

Figure 1. Maculopapular rash on the trunk.

and periadnexal infiltration of the hemopoietic cells in the dermis, without the involvement of the epidermis. The cells had scant, basophilic cytoplasm and euchromatic nuclei without prominent nucleoli. Some of the nuclei had convoluted nuclear membranes. Further immunohistochemical evaluation showed that these cells expressed CD45, CD15, CD68 and lysozyme. The cells were negative for CD3, CD5, CD20, CD34, Pax-5, TdT, CD117, myeloperoxidase (MPO) and mast cell tryptase. The immunohistochemical features indicated dermal infiltration by acute leukemia of monocytic lineage by cells with a monocytic differentiation (Figure 2). Following the histology of the skin biopsy, she was referred to a hematologist and a complete hematological work-up including a bone marrow biopsy was planned.

A bone marrow biopsy showed marked hypercellularity and hematopoiesis was largely impaired. The majority of the cells were blasts (70%) which contained scanty nongranular, basophilic cytoplasm, with oval or lobular nuclei without nucleoli. These blast cells expressed lysozyme, CD68+/- and CD15+/-, but not CD3, CD20, CD34, CD61, CD117, TdT or MPO. There was no increase in CD34 positive blasts. The genetic analysis of bone marrow cells revealed a normal karyo-

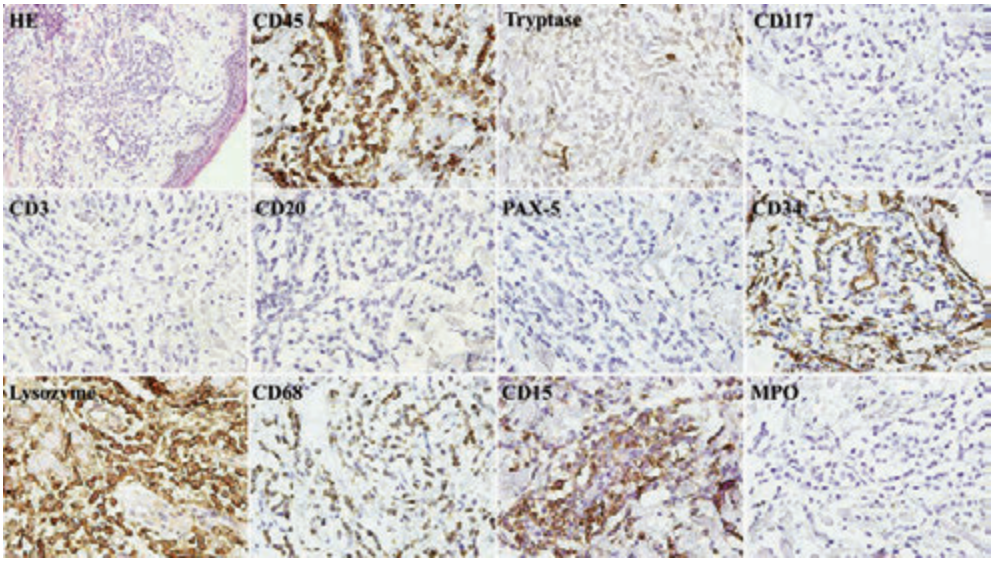

Figure 2. The skin biopsy specimen of the lesion showed perivascular, monomorphous infiltrates of atypical monocytic cells in the dermis (hematoxylin-eosin stain, HEx200). Immunohistochemical features: the cells were positive for CD45, CD15, CD68 and lysozyme and negative for CD3, CD20, CD34, Pax-5, CD117, myeloperoxidase (MPO) and mast cell tryptase (x400).

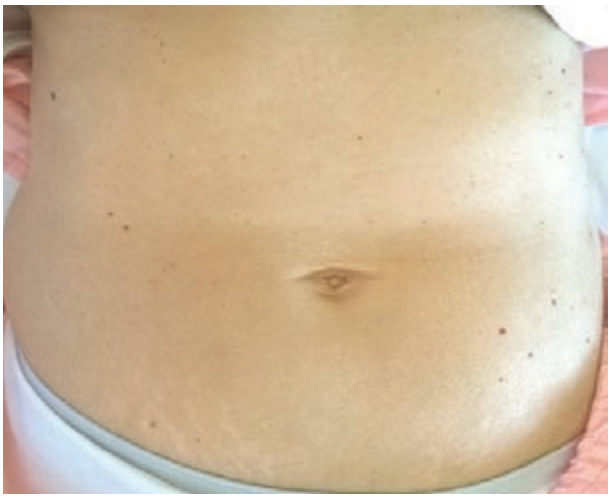

Figure 3. Skin lesions completely disappeared after induction and consolidation chemotherapy.

type, 46XX and FLT3/ITD gene mutations were not detected.

Immunophenotypic analysis of peripheral blood by flow cytometry detected 25% monocytoid cells within CD45 positive population (leukocytes). The cells expressed CD4, CD11b, CD11c (bright), CD13, CD14, CD16, CD33, CD34, CD36, CD38 and HLA-DR. These findings were compatible with acute monocytic leukemia (French-American-British (FAB) AML-M5b). Therefore, the diagnosis of acute monocytic leukemia (FAB AML-M5b) was made.

The patient received the standard 3 + 7 induction chemotherapy for acute monocytic leukemia including cytarabine 100 mg/m2 daily on days 1–7 and daunorubicin 50 mg/m2 daily on days 1–3 and, subsequently, high-dose cytarabine (HiDAC) consolidation therapy. Her skin lesions completely disappeared during chemotherapy (Figure 3).

Discussion

Leukemia cutis is the term used for cutaneous manifestations of leukemia, which can have varied clinical presentations. Epidemiological data on the prevalence and incidence of leukemia cutis are scarce (4). Overall, leukemia cutis occurs in 2.1% to 30% of leukemia patients depending on the underlying form of leukemia (4). Most frequently leukemia cutis has been described in patients with acute myeloid leukemia. The analysis of the data from 381 patients with acute myeloid leukemia was performed by Agis et al (2002). They showed that the prevalence of leukemia cutis was 3.7% (14 patients). The majority of patients with leukemia cutis (71.4% or 10/14 cases) had FAB M4 and M5 subtypes. Similar results have been reported by other authors (50% and 72.2%) (7, 8). Skin involvement can also be seen in patients with chronic myeloproliferative disease, including myelodysplastic syndrome, chronic lymphocytic leukemia, and chronic myeloid leukemia (4, 6, 9). Our patient was diagnosed with acute monocytic leukemia (FAB-M5b). Therefore, FAB4 and FAB5 are of particular interest to dermatologists because skin changes are most commonly seen in these forms of leukemia (4). The age and sex distribution of patients with leukemia cutis do not differ from leukemia patients without cutaneous involvement (4, 8, 10).

Leukemia cutis displays a variety of clinical appearances. Patients with leukemia cutis may have single or multiple skin lesions (6, 11). The lesions are usually described as violaceous, erythematous, or hemorrhagic nodules, papules, vesicles, bullae and plaques (6, 12). In terms of size, the lesions may be several millimeters or as large as the palm of the hand (4). In the retrospective study of 75 patients with leukemia cutis performed by Kang et al. (2013), the three most common types of leukemia cutis lesions were nodules (33%), papules (30%), and plaques (17%). Vesicles, ulcer, and swelling were uncommon findings of leukemia cutis. Nodules were the most common lesion in acute granulocytic leukemia, acute myelomonocytic leukemia and acute lymphocytic leukemia, whereas papules were most frequently seen in acute monocytic leukemia and chronic myeloid leukemia (2). A particular type of leukemia can produce different skin lesions during the course of the disease, even in the same patient (6, 11). The skin lesions are located most commonly in extremities, followed by trunk, scalp, and face (2, 4, 6, 9). Some studies have shown that there are no predilection sites of leukemia cutis according to leukemia type (2, 4, 11, 13). In contrast, Kang et al. (2013) reported that acute monocytic leukemia, chronic myeloid leukemia and acute granulocytic leukemia lesions were most frequently found on the extremities (63%, 44%, 42%, respectively); however, acute lymphocytic leukemia

occurred mainly on the trunk (44%). In addition, leukemia cutis can occur at the sites of previous or concomitant inflammation such as herpetic lesions, trauma, intravenous catheters, recent surgical sites, and so forth (3, 6, 14, 15). Our patient had erythematous macules and papules distributed on the trunk, thighs and upper arms.

The time between diagnosing the systemic leukemia and the occurrence of leukemia cutis varies (4). It has been reported that in the most patients (55-77%) leukemia cutis develops after leukemia has been diagnosed and, sometimes, it may be the first sign of relapse (2, 4). Concurrent cutaneous and systemic manifestation of leukemia have been observed in about one third (23-38%) of the patients (2, 4). In less than 10% of cases, leukemia cutis may occur several months or years before bone marrow or peripheral blood involvement and without systemic symptoms (2, 4, 16, 17). This type of leukemia cutis is termed “aleukemic leukemia cutis” or “primary extramedullary leukemia”. In our case, leukemia cutis was a presenting sign of acute monocytic leukemia.

The diagnosis of leukemia cutis is based on the evaluation of the morphologic pattern of skin infiltration, cytologic findings, and, most importantly, the immunohistochemical characteristics of the tumor cells (4, 6). The correlation with clinical data and hematologic results from the peripheral blood and bone marrow is often helpful to make the conclusive diagnosis. In general, most types of leukemic skin infiltrates show a perivascular and/or periadnexal distribution with well-defined boundary, as in our patient, or dense diffuse infiltrate involving the dermis and subcutis. It is impossible to determine the type of underlying leukemia based on histologic findings alone. In addition, in the absence of systemic leukemia, leukemia cutis can be difficult to distinguish from other malignant conditions, such as non-Hodgkin lymphoma (9). Therefore, immunohistochemistry is very important for establishing a specific, clinically useful diagnosis (6, 18, 19). It may be helpful to use myeloid, T-cell and B-cell markers such as MPO, lysozyme, CD68, CD34, CD117, TdT, CD10, CD15, PAX-5, CD3, CD4, CD8, CD1a, CD5, CD19, CD20 to the cell of origin and confirm the diagnosis (6, 18). However, it is not possible to classify the different forms of leukemia by skin biopsy alone; additional immunophenotyping and molecular genetic examinations (e.g., peripheral blood, bone marrow biopsy) are needed (4). In our case leukemic cells in cutis expressed CD45, CD15, CD68 and lysozyme which corresponded to myeloid differentiation. However, we confirmed the diagnosis by immunophenotypic analysis of peripheral blood and microscopic examination of bone marrow biopsy.

Conclusion

The clinical appearances of leukemia cutis are highly variable and include nodules, papules, maculae, and plaques. Leukemia cutis may occur after, before or at the same time as the diagnosis of leukemia. In the present case, the maculopapular rash was the first clinical sign pointing to the diagnosis of leukemia. Therefore, a skin biopsy with subsequent histopathological and immunohistochemical examination is the method of choice for early diagnosis. We suggest that leukemia cutis may be considered in the differential diagnosis of maculopapular rash on the trunk and legs. In addition, interdisciplinary dermatologic and hematologic follow-up is very important, even for patients in remission with underlying leukemic disease for prompt identification of cutaneous recurrences.

References

1. Cronin DM, George TI, Sundram UN. An updated approach to the diagnosis of myeloid leukemia cutis. Am J Clin Pathol. 2009;132(1):101-10.
2. Kang YS, Kim HS, Park HJ, Lee JY, Kim HO, Cho BK, et al. Clinical characteristics of 75 patients with leukemia cutis. J Korean Med Sci. 2013;28(4):614-9.
3. Narayanan G, Sugeeth MT, Soman LV. Mixed phenotype acute leukemia presenting as leukemia cutis. Case Rep Med. 2016;2016:1298375.
4. Wagner G, Fenchel K, Back W, Schulz A, Sachse MM. Leukemia cutis - epidemiology, clinical presentation, and differential diagnoses. J Dtsch Dermatol Ges. 2012;10(1):27-36.
5. Chao SC, Lee JY, Tsao CJ. Leukemia cutis in acute lymphocytic leukemia masquerading as viral exanthem. J Dermatol. 1999;26(4):216-9.
6. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. Am J Clin Pathol. 2008;129(1):130-42.
7. Baer MR, Barcos M, Farrell H, Raza A, Preisler HD. Acute myelogenous leukemia with leukemia cutis. Eighteen cases seen between 1969 and 1986. Cancer. 1989;63(11):2192-200.

8. Kaddu S, Zenahlik P, Beham-Schmid C, Kerl H, Cerroni L. Specific cutaneous infiltrates in patients with myelogenous leukemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. J Am Acad Dermatol. 1999;40(6 Pt 1):966-78.
9. Grunwald MR, McDonnell MH, Induru R, Gerber JM. Cutaneous manifestations in leukemia patients. Semin Oncol. 2016;43(3):359-65.
10. Agis H, Weltermann A, Fonatsch C, Haas O, Mitterbauer G, Mullauer L, et al. A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. Ann Hematol. 2002;81(2):90-5.
11. Watson KM, Mufti G, Salisbury JR, du Vivier AW, Creamer D. Spectrum of clinical presentation, treatment and prognosis in a series of eight patients with leukaemia cutis. Clin Exp Dermatol. 2006;31(2):218-21.
12. Sharma SK, Gupta S, Seth T, Mishra P, Mahapatra M, Singh MK, et al. Leukemia cutis: an unusual presentation. Indian J Hematol Blood Transfus. 2012;28(3):175-7.
13. Willard RJ, Turiansky GW, Genest GP, Davis BJ, Diehl LF. Leukemia cutis in a patient with chronic neutrophilic leukemia. J Am Acad Dermatol. 2001;44(2 Suppl):365-9.
14. Lee JI, Park HJ, Oh ST, Lee JY, Cho BK. A case of leukemia cutis at the site of a prior catheter insertion. Ann Dermatol. 2009;21(2):193-6.
15. Rao AG, Danturty I. Leukemia cutis. Indian J Dermatol. 2012;57(6):504.
16. Hejmadi RK, Thompson D, Shah F, Naresh KN. Cutaneous presentation of aleukemic monoblastic leukemia cutis - a case report and review of literature with focus on immunohistochemistry. J Cutan Pathol. 2008;35 Suppl 1:46-9.
17. Ohno S, Yokoo T, Ohta M, Yamamoto M, Danno K, Hamato N, et al. Aleukemic leukemia cutis. J Am Acad Dermatol. 1990;22(2 Pt 2):374-7.
18. Cibull TL, Thomas AB, O'Malley DP, Billings SD. Myeloid leukemia cutis: a histologic and immunohistochemical review. J Cutan Pathol. 2008;35(2):180-5.
19. Hussein MR, Al bshabshe AA, Dalati T. Leukemia cutis: case report and review of literature. Appl Immunohistochem Mol Morphol. 2010;18(2):190-1.

Leukemija kože – prikaz slučaja

Sažetak

Leukemiju kože karakteriše difuzna infiltracija kože neoplastičnim ćelijama. Može se javiti kod svih vrsta leukemija u vidu različitih kožnih promena kao što su makule, papule, noduli, plakovi i ulkusi. U ovom radu je prikazana bolesnica starosti 52 godine, sa eritematoznim makulama i papulama na trupu, natkolenicama i nadlakticama. Biopsija kože je pokazala monomorfnu, perivaskularnu i periadneksalnu infiltraciju ćelijama koje su pozitivne na CD45, CD15, CD68 i lizozim. Naknadnom biopsijom koštane srži i imunofenotipskom analizom ćelija periferne krvi postavljena je dijagnoza akutne monocitne leukemije (FAB AML-M5b). Kod ove bolesnice, prvi klinički znak leukemije bio je makulopapularni osip. Stoga predlažemo da se leukemija kože može razmotriti u diferencijalnoj dijagnozi makulopapularne ospe na trupu i ekstremitetima.

Ključne reči: Akutna monocitna leukemija; Kožne neoplazme; Egzantem; Diferencijalna dijagnoza; Prikazi slučajeva

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Concurrence of Bullous Pemphigoid and Psoriasis: A Case Report

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Abstract

Bullous pemphigoid (BP) and psoriasis are chronic recurrent inflammatory skin diseases. The pathogenesis of concurrence of BP with psoriasis is still unknown. A 39-year-old male with a five-year history of chronic plaque psoriasis developed itchy large tense bullae on the trunk and upper extremities after he had been receiving narrow band ultraviolet B (NBUVB) therapy over five months. Skin biopsy from bulla on the trunk showed typical histological features of BP. Direct immunofluorescent staining showed deposit of immunoglobulin G and C3 in the basement membrane zone (BMZ) which supported the diagnosis of BP. It has been postulated that the autoimmune process responsible for BP lesions might be induced by ultraviolet light therapy and/or the inflammatory processes that occur in psoriasis.

Key words: Pemphigoid, Bullous; Psoriasis; Skin Diseases; Comorbidity; Diagnosis; Case Reports

Introduction

Bullous pemphigoid (BP) is an autoimmune disease characterized by multiple tense blisters arising on normal or erythematous skin with a predilection for flexural areas (1-3). Autoimmunity has been established as the etiology of BP, which presents as immunoglobulin G (IgG) and C3 deposits along the epidermal basement membrane zone (BMZ) (1, 2). Another common skin autoimmune disease is psoriasis, a condition characterized by erythematous plaques with silvery white scales. The most common affected areas are scalp, elbows, knees, and lumbosacral region. Environmental trigger factors such as trauma, medications, and infections, in addition to immunological and genetic factors, appear to play a role in the pathogenesis of psoriasis (4).

The pathogenesis of BP in concurrence with psoriasis is still unknown. The trigger factors responsible for the concurrence of these two diseases has been reported previously such as photochemotheraphy of psoralen ultraviolet A (PUVA) (6) and narrow band-ultraviolet B (NB-UVB). This suggests that psoriasis as a chronic inflammatory disease and the effect of the local ultraviolet radiation provides a particular predisposition of the immune system leading to autoimmune response such as developing BP lesions (5). We report a case of BP in a patient who suffers from psoriasis vulgaris that might be induced by NB-UVB.

Case Report

A 39-year-old male presented with pruritic, large tense bullae on the trunk and upper extremities which had appeared two weeks before admission. Initially, the blisters developed on the arms, then spread into other parts of the body. The patient had had chronic plaque psoriasis for five years. In addition to methotrexate and topical corticosteroids administration, the patient received NB-UVB for psoriasis. After five months of this treatment, he developed multiple bullae on his trunk and extremities. Physical examination revealed tense bullae on the abdomen, upper, and lower limbs. The Nikolsky sign was negative. There were erythematous scaly plaques on the lower extremities and the blisters also ap-

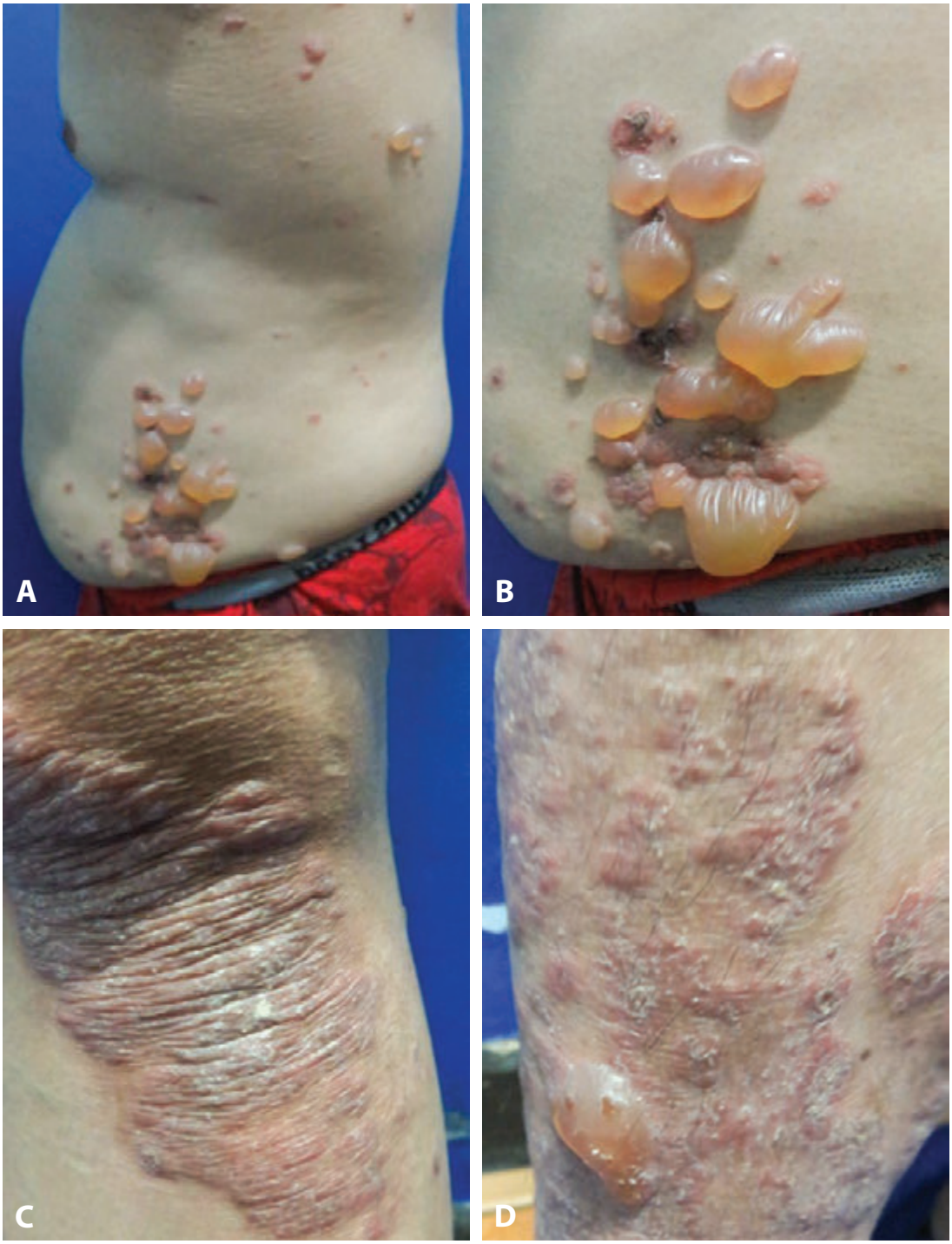

Figure 1. A, B. Blisters on the trunk. 1. C, D. Scaly plaques with blister on the lower extremity.

peared over the scaly plaques (Fgure 1. A-D). The skin biopsy from erythematous scaly plaque showed psoriasiform reaction with parakeratosis, acanthosis, and elongated rete ridges,which supported the diagnosis of psoriasis (Figure 2. A). Histopathological examination from bullae on the trunk revealed a sub-epidermal blister containing eosinophils (Figure 2.B). Direct immunofluorescence (DIF) from perilesional skin showed a linear depos-

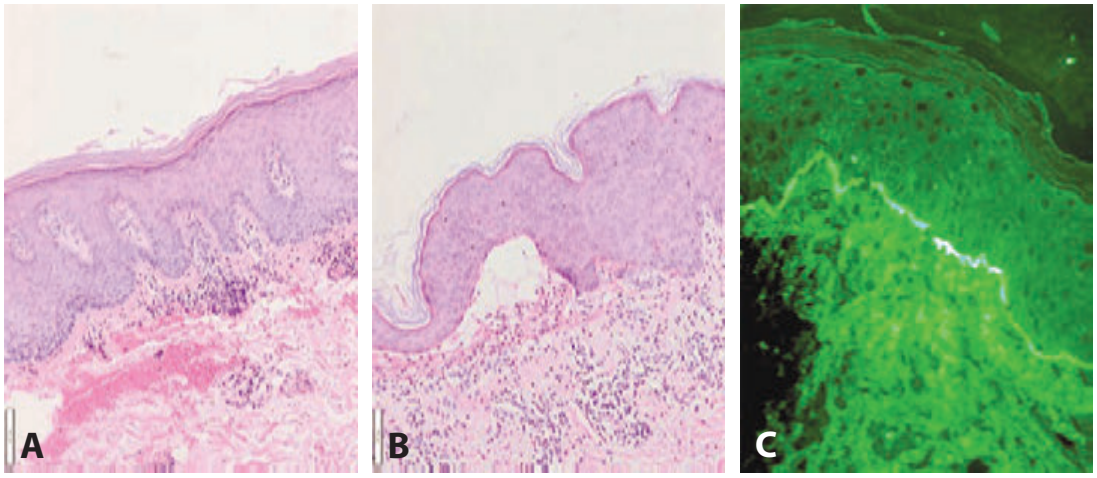

Figure 2. A). Psoriasiform reaction with parakeratosis, acanthosis, and elongation of rete ridges B). Subepidermal blisters containing eosinophils, C). Linear deposit IgG and C3 at BMZ.

it IgG and C3 at BMZ (Figure 2.C) which provided the evidence of BP.

The patient was therefore treated with 15 mg methotrexate/week orally, 64 mg of prednisone (1 mg/kgBW/day), and topical desoximethason 0.25% cream. The NB-UVB phototherapy was discontinued. At one-month follow-up, psoriatic lesion improved (Table 1) and at three-month follow-up, both conditions subsided, leaving only post-inflammatory pigmentation.

Discussion

Several cases of psoriasis and autoimmune bullous diseases have been reported; however, the relationship between two diseases remains unknown (7). In most cases, psoriasis precedes the onset of autoimmune bullous disease with an average interval of 20 years (8). In this case, psoriasis developed approximately five years before BP.

In BP patients, there is an auto-reactive response of T cells and B cells to BP antigen 1 (BPAG1/230 kDa) and BPAG2 antigens (180 kDa) (9). Several precipitating factors such as ultraviolet (UV) exposure, radiation therapy, trauma, drugs, malignancy, and autoimmune diseases have been reported to be associated with BP (10).

The mechanism of coexistence of psoriasis and BP in one patient is unclear (5). It is still the subject of controversy whether it is due to the treatment of psoriasis, pathological events at the basement membrane zone (BMZ) in psoriasis itself, common immunological or immunogenetic mechanisms, or a coincidence of multiple factors precipitating the autoimmune bullous diseases (11). A reduced barrier function of the psoriatic epidermis combined with the irritant effects of therapies administered for psoriasis may precipitate blister formation (1). Among different antipsoriatic therapies, UV radiation is most commonly suspected of triggering BP. It is suggested that UV radiation may precipitate BP by immunological alteration of the epidermal antigens. The result is formation of complement-binding anti-BMZ antibodies leading to bullous skin lesions (6). Washio, et al. (12)

Table 1. Follow up of PASI and BPDAI after treatment

Week	I	II	III	IV	V	VI	VII	VIII
PASI	5,7	4,8	2,4	1,2	0	0	0	0
BPDAI (bullae/erosion)	24	20	16	12	6	0	0	0

PASI: psoriasis area severity index, BPDAI: Bullous Pemphigoid Disease Area Index

suggested alterations of the BMZ antigenicity by UV radiation that might lead to the release of antigens and consequently stimulation of autoantibody production. The development of bullous lesions in this psoriasis patient suggested that NB-UVB radiation could have provoked subclinical BP.

The diagnosis of autoimmune bullous disease is based on clinical features, histopathological examination, and DIF (13). The clinical features of BP are large tense bullae in predilection site and negative Nikolsky sign (14). Histopathological examination of BP shows a sub-epidermal blister with characteristic infiltrates containing eosinophils (3, 14). DIF is a laboratory examination that has become the gold standard for the diagnosis of autoimmune bullous disease (7). DIF of BP lesion revealed a linear arrangement of IgG and C3 deposits in BMZ (15). In this case, the DIF examination showed a linear deposit of IgG and C3 in the dermo-epidermal junction.

The diagnosis of psoriasis is based on clinical manifestation and histopathological examination, especially in difficult cases (15). Histopathological features of advanced psoriasis are psoriasiform hyperplasia with acanthosis, elongation of rete ridges, parakeratosis, hypogranulosis, and microabses of Munro (17). In this case, the patient had suffered from psoriasis for the last five years, as confirmed by histopathological examination.

There are some alternative therapeutic modalities for patients with coexisting BP and psoriasis. Immunosupressive drugs proved to be effective in both diseases (18), such as methotrexate (19), cyclosporine (20), combination of low-dose cyclosporine and low dose systemic steroids (21), dapsone (22), azathioprine (23), mycophenolate mofetil (24), and acitretin (25). A combination of methotrexate and systemic corticosteroid for these two diseases has never been reported. The combination treatment was effective in this patient, since after the long-term follow-up there were no side effects.

Conclusion

In conclusion, the pathogenesis of concurrent BP and psoriasis remains unknown. One of the possible causes of BP in concurrence with psoriasis is that UV radiation might alter BMZ antigenicity and release altered antigens that might result in the stimulation of antibody against the BMZ. Due to the fact that BP and psoriasis are immunologically mediated, a combination of immunosuppressive regimens directed at cellular and humoral factors usually results in clinical improvement.

References

1. Barnadas MA, Gilaberte M, Pujol R, Agustí M, Gelpí C, Alomar A. Bullous pemphigoid in a patient with psoriasis during the course of PUVA therapy: study by ELISA test. Int J Dermatol. 2006;45(9):1089-92.
2. Wang TS, Tsai TF. Remission of bullous pemphigoid after rituximab treatment in a psoriasis patient on regular low dose methotrexate. Acta Derm Venereol. 2014;-94(1):108-9.
3. James WD, Berger TG, Elston DM, editors. Andrews' disease of the skin, clinical dermatology. 11th ed. London: Saunders/Elsevier; 2011. p. 455-7.
4. Bloom D. Psoriasis with superimposed bullous eruption. Med J Rec. 1929;130:246-8.
5. Cvetković Jordanov L, Kandolf Sekulović L, Mijušković Ž, Zolotarevski Z, Zečević R. Concomitant psoriasis and bullous pemphigoid - a case report. Serbian Journal of Dermatology and Venereology. 2014;6(1):30-8.
6. Abel EA, Bennett A. Bullous pemphigoid. Occurrence in psoriasis treated with psoralens plus long-wave ultraviolet radiation. Arch Dermatol. 1979;115(8):988-9.
7. Ohata C, Ishii N, Koga H, Fukuda S, Tateishi C, Tsuruta D, et al. Coexistence of autoimmune bullous diseases (AIBDs) and psoriasis: a series of 145 cases. J Am Acad Dermatol. 2015;73(1):50-5.
8. Stoica LE, Patrascu V, Dascalu RC, Ciurea ME. Bullous pemphigoid associated with psoriasis, breast cancer and Parkinson's disease. Curr Heatlh Sci J. 2014;40 (1):62-5.
9. Fuertes de Vega I, Iranzo-Fernández P, Mascaró-Galy JM. Bullous pemphigoid: clinical practice guidelines. Actas Dermosifiliogr. 2014;105(4):328-46.
10. Borradori L, Bernard P. Pemphigoid group. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. 3rd ed. London: Elsevier; 2012. p. 475-82.
11. Kirtschig G, Chow ET, Venning VA, Wojnarowska FT. Acquired subepidermal bullous diseases associated with psoriasis: a clinical, immunopathological and immunogenetic study. Br J Dermatol. 1996;135(5):738-45.
12. Washio H, Hara H, Suzuki H, Yoshida M, Hashimoto T. Bullous pemphigoid on psoriasis lesions after UVA radiation. Acta Derm Venereol. 2005;85(6):561-3.
13. Rotaru M, Opris A. Update and literature review of treatment and prognosis factors in bullous pemphigoid. acta Medica Transilvanica. 2015;20(2):52-4.
14. Culton DA, Liu Z, Diaz LA. Bullous pemphigoid. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's dermatology in general medicine. 8th ed. New York: McGraw-Hill; 2012. p. 608-16.
15. Jukić IL, Marinović B. Significance of immunofluorescence in the diagnosis of autoimmune bullous dermatoses. Clin Dermatol. 2011;29(4):389-97.

16. Gudjonsson JE, Elder JT. Psoriasis. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's dermatology in general medicine. 8th ed. New York: McGraw-Hill; 2012. p. 197-231.
17. Griffiths CEM, Barker JNWN. Psoriasis. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's textbook of dermatology. 8th ed. Wiley-Blackwell; 2010. p. 20.1-54.
18. Roeder C, Driesch PV. Psoriatic erythroderma and bullous pemphigoid treated successfully with acitretin and azathioprine. Eur J Dermatol.1999;9(7):537-9.
19. Lesniewska A, Kalinska-Bienias A, Kowalewski C, Schwartz R, Wozniak K. Development of bullous pemphigoid in a patient with psoriasis and metabolic syndrome. Cutis. 2016;98(3):E19-23.
20. Boixeda JP, Soria C, Medina S, Ledo A. Bullous pemphigoid and psoriasis: treatment with cyclosporine. J Am Acad Dermatol. 1991;24(1):152.
21. Bianchi L, Gatti S, Nini G. Bullous pemphigoid and severe erythrodermic psoriasis: combined low-dose treatment with cyclosporine and systemic steroids. J Am Acad Dermatol. 1992;27(2 Pt 1):278.
22. Hisler BM, Blumenthal NC, Aronson PJ, Hashimoto K, Rudner EJ. Bullous pemphigoid in psoriatic lesions. J Am Acad Dermatol. 1989;20(4):683-4.
23. Primka EJ 3rd, Camisa C. Psoriasis and bullous pemphigoid treated with azathioprine. J Am Acad Dermatol. 1998;39(1):121-3.
24. Nousari HC, Sragovich A, Kimyai-Asadi A, Orlinsky D, Anhalt GJ. Mycophenolate mofetil in autoimmune and inflammatory skin disorders. J Am Acad Dermatol. 1999;40(2 Pt 1):265-8.
25. Kobayashi TT, Elston DM, Libow LF, David-Bajar K. A case of bullous pemphigoid limited to psoriatic plaques. Cutis. 2002;70(5):283-7.

Istovremena pojava buloznog pemfigoida i psorijaze – prikaz slučaja

Sažetak

Bulozni pemfigoid (BP) i psorijaza su hronične recidivne inflamatorne kožne bolesti. Još nije poznata patogeneza istovremene pojave buloznog pemfigoida i psorijaze. Tridesetdevetogodišnji muškarac, koji je imao hroničnu plak psorijazu pet godina, dobio je veliku čvrstu bulu koja svrbi na trupu i gornjim ekstremitetima nakon što je primao ultraljubičastu B-terapiju uskog opsega pet meseci. Biopsija kože iz bule sa trupa pokazala je tipične histološke odlike buloznog pemfigoida. Direktno imunofluorescentno bojenje pokazalo je deponovanje imunoglobulina G i C3 u bazi membranske zone (BMZ) što je potvrdilo dijagnozu buloznog pemfigoida. Pretpostavlja se da bi se autoimuni proces koji je odgovoran za bulozni pemfigoid lezije mogao izazvati ultraljubičastom svetlosnom terapijom i/ili inflamatornim procesima koji se dešavaju u psorijazi.

Ključne reči: Bulozni pemfigoid; Psorijaza; Kožne bolesti; Komorbiditet; Dijagnoza; Prikazi slučajeva

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Terra Firma Forme Dermatosis – a Report of two Cases and a Review of the Literature

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Abstract

Terra firma-forme dermatosis (TFFD) or Duncan's dirty dermatosis is a bizarre, acquired, and idiopathic dermatosis. It is characterized by its asymptomatic, yellowish, or brownish dirt-like lesions, resistant to usual washing with soap and water, but disappearing when rubbed with 70% ethyl alcohol or isopropyl alcohol. Swabbing with alcohol is both diagnostic and therapeutic means for this disorder. We present two boys, aged 14 and 11, with asymptomatic brownish, dirt-like lesions on the chest and forearms, respectively. Skin lesions were continuously present for more than a month. Both of the patients had usual hygiene habits. The diagnosis of TFFD was confirmed by rubbing with 70% ethyl alcohol which led to disappearance of the lesions. TFFD often causes much concern in patients and parents of affected children. Since its clinical picture is similar to some other dermatoses, the disease can be misdiagnosed. Therefore, it is important to recognize this dermatosis in dermatological and pediatric practice in order to explain the benign nature of the disease to patients and to avoid unnecessary diagnostic tests.

Key words: Hyperpigmentation; Skin Diseases; Ethanol; Diagnosis; Therapeutics; Case Reports

Introduction

Terra firma-forme dermatosis (TFFD) was first described in 1987 as Duncan's dirty dermatosis. The name "terra firma" is derived from Latin words meaning "solid earth or land" (1, 2). It is characterized by its yellowish or brownish dirt-like asymptomatic patches or plaques caused by disorder of keratinization of unknown origin. Although the patients have regular washing habits, skin changes in TFFD cannot be removed by conventional washing with water and soap, and they cause concern in patients. TFFD is an uncommon condition, rarely mentioned in literature. However, the disease is probably more widespread among patients than literature shows since it is commonly misdiagnosed and unreported (2-5).

Case Report

Case 1. A 14- year old boy was presented with asymptomatic dirt-like hyperpigmentation on the sternum and upper chest, which had been present for about 1 month. The boy had a history of regular washing habit with soap and water. The patient was otherwise healthy, with no reported history of other diseases, trauma, eczema or excessive use of cosmetic products. Dermatological examination revealed dirt-like hyperpigmented patches on the sternum and upper chest (Figure 1). The lesions disappeared after rubbing with 70% ethyl alcohol, leaving frictional erythema (Figure 2).

Case 2. A 11-year-old boy was presented with asymptomatic brownish lesions on the forearms, with a presumed diagnosis of atopic dermatitis. These lesions were constantly present during the previous four months despite regular washing with water and soap. He did not have any other diseases neither did he use topical corticosteroids and moisturizing creams. Dermatological examination revealed papillomatous hyperpigmented patches on the forearms, more prominent on the left side (Figure 3). The diagnosis of TFFD was confirmed by rubbing the patches with

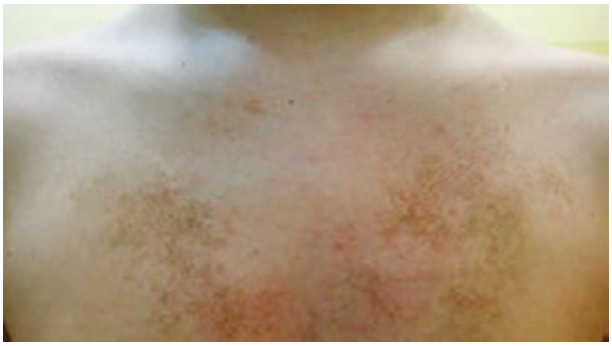

Figure 1 A. The initial appearance of hyperpigmented patch lesions on the sternum and upper chest in a 14-year-old-boy.

70% ethyl alcohol gauze pad, which led to the disappearance of lesions.

Discussion

TFFD was defined by Duncan et al. as a rare disorder of keratinization of unknown etiology (1). It occurs in people of different ages, with higher frequency reported among children and young adults and with similar frequency in both sexes (1-3, 5, 6). In a retrospective study done by Asslan et al. which was published in 2018, out of 79 patients with TFFD 88.6% were children whose average age was 10.4 years. A slightly higher incidence was found in females (64.6%) (7). Similar results were reported by Berk et al.: out of the 31 patients reported, 54.8% were females, while 55% were children whose average age was 12 years (8). Both of our patients were also under 17 years of age.

According to literature data the duration of TFFD ranges from 3 weeks to several years (2, 8, 10, 11,12). In case of our patients, the diagnosis of TFFD was set one and four months after the appearance of skin changes. In the study of Berk, the median duration of lesions before presentation was 4 months. Many cases were diagnosed in a short period of time, which confirms that the disease is more frequent than the literature data show (8).

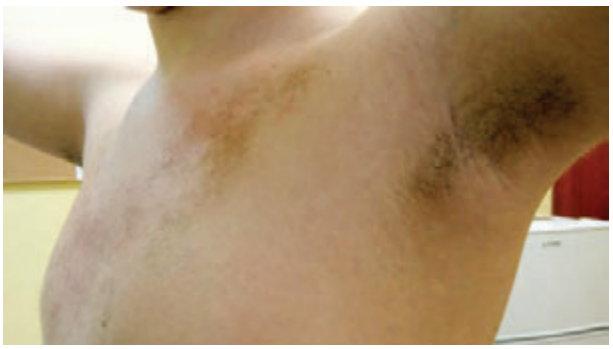

Figure 1 B. Resolution of lesions and frictional erythema after rubbing with 70% ethyl alcohol pads

The etiology of TFFD is still unclear (1-3, 9-12). Some authors presume that this condition is caused by a delay in keratinocyte maturation, which leads to the retention of keratinocytes and melanin within the epidermis. This disordered keratinocyte buildup and compaction of scales, sebum and dirt that may ultimately lead to the hyperkeratosis and hyperpigmentation clinically manifests as TFFD (3-5, 8, 12). Although the genetic predisposition to TFFD was described in the literature, it is not clearly established in most of the studies (2, 3, 10-13). In the study of Asslan et al two patients were siblings and had xerosis, which may lead to a suspicion of the possible impact of inheritance on the occurrence of this disease, but more extensive studies are needed to confirm these assumptions (7). As a possible cause of TFFD, Ashique et al. emphasize inadequate hygiene and inappropriate care of skin areas damaged by previous surgical interventions (13). Most of other authors did not establish a relationship of TFFD with poor hygiene or hygienic habits (3, 10, 12, 13). Patients often state that the changes occurred during warm periods and sometimes due to the intense exposure to the sun (1, 8, 10, 12, 14).

TFFD usually presents on the neck, face, trunk and ankles (1, 2, 7, 8, 12). In our Case 1, the changes were localized on the chest, whereas in Case 2 they were localized on the forearms, which is rarely described in the literature (7, 14). In the study of Aslan and al. the most common location of lesion was the trunk (27.8%) and extremities (26.6%). In the same study the TTFD lesions were multiple in 34.2% of patients and in 77.2% of patients they were symmetrical (7). As the most common localization of TFFD, Berk reported the neck, in 21 patients (67.77%), then the ankles and face. Lesions were mainly symmetrical (8). This dermatosis can also occur on scars after surgical interventions, scalp, arms, and legs, or postauricular, axillary, umbilical and pubic areas (2, 4, 6, 8-10, 12, 15).

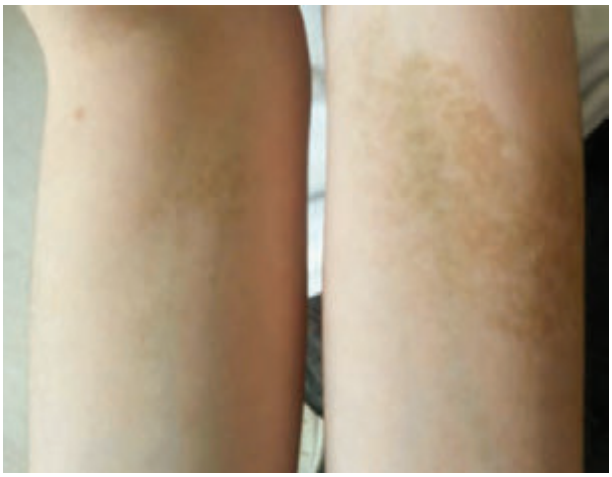

Figure 2. Brownish plaques on the forearms in an 11-year-old boy.

Clinically, TFFD is usually presented as asymptomatic yellowish or brownish dirt-like plaques. The changes may also have papilomatosus, verrucous or reticular appearance (3, 11). In our Case 1, the changes were in the form of hyperpigmented patch lesions while in Case 2 they were papillomatous plaques. In both patients, they could not be removed by usual washing with water and soap, which made their parents worried. After rubbing the lesions with 70% ethyl alcohol, the lesions disappeared, which confirmed the diagnosis of TFFD (2, 3, 8, 12).

It is important to distinguish TFFD from other similar dermatoses and thus avoid unnecessary invasive testing and biopsy of the skin (3, 7, 8, 12, 13). To confirm the diagnosis, a test with 70% ethyl alcohol or isopropyl alcohol is sufficient (2, 3, 7, 8, 11, 12). In recent literature it is mentioned that dermoscopy can assist in the evaluation of TFFD. Dermoscopic changes pointing to this dermatosis are in the form of unstructured, large polygonal platlike brown to black macules or scales, arranged in a mosaic or tile-like pattern, interrupted in furrows (10). Biopsy is rarely necessary. Characteristic histology of TFFD shows the prominent lamellar hyperkeratosis with compact orthokeratotic whorls, prominent keratin globules in the stratum corneum, increased melanin in the basal layer, papillomatosis and acanthosis (1, 2, 9-12).

TFFD should be distinguished from dermatosis neglecta, acantosis nigricans, “dirty neck” of atopic dermatitis, confluent and reticulate papillomatosis, pityriasis versicolor, ichthyosis, seborrheic dermatitis, seborrheic keratosis and epidermal nevus (2, 4, 7-9, 11, 12). The most common differential diagnostic problem is the differentiation of TFFD from dermatosis neglecta, as skin changes in TFFD can also appear as dirt, even though the patient has regular hygienic habits. Dermatosis neglecta is typical among people of all ages with poor hygienic habits, but these changes may disappear after simple bathing with water and soap, unlike TFFD (2, 4, 9, 15).

Lesions in acanthosis nigricans are darker and smoother, usually localized on the back of the head, sides of the neck, and in skin folds. This condition is commonly associated with obesity, hyperinsulinemia and rarely with malignant diseases. Skin lesions cannot be removed by washing with water and soap or by rubbing with a gauze soaked in 70% ethyl alcohol or isopropyl alcohol (2, 10, 13, 15). Atopic dermatitis localized on the neck, the so-called “Dirty neck syndrome”, is more common among adult patients in the form of plaques and cannot be removed by rubbing with alcohol pads (8). Confluent and reticulate papillomatosis are characterized by confluent, flat, brown papules forming a pigmented reticulated pattern, localized primarily in the intermammary, epigastric and interscapular region (2).

It is sufficient to rub skin changes with 70% ethyl alcohol or isopropyl alcohol in order to diagnose as well as to treat TFFD (2, 3, 8, 11, 12). Chun et al. reported successful treatment of TFFD localized on the face with 20% salicylic acid in the alcohol (16).

Conclusion

This disease can be diagnosed and treated at the same time by recognizing the TFFD clinical presentation and performing a test with 70% ethyl alcohol or isopropyl alcohol. It is important to recognize this dermatosis so that its benign nature can be explained to the patients and thus to avoid unnecessary diagnostic tests, as well as the patient’s concern.

Abbreviatioins

TFFD - Terra firma forme dermatosis

References

1. Duncan WC, Tschen JA, Knox JM. Terra firma-forme dermatosis. Arch Dermatol. 1987;123(5):567-9.
2. Akkash L, Badran D, Al-Omari AQ. Terra firma-forme dermatosis. Case series and review of the literature. J Dtsch Dermatol Ges. 2009;7(2):102-7.
3. Greywal T, Cohen PR. Terra firma-forme dermatosis: a report of ten individuals with Duncan's dirty dermatosis and literature review. Dermatol Pract Concept. 2015;5(3):29-33.
4. Martin-Gorgojo A, Alonso-Usero V, Gavrilova M, Jorda-Cuevas E. Dermatosis neglecta or terra firma-forme dermatosis. Actas Dermosifiliogr. 2012;103(10):932-4.
5. Naveen KN, Hegde S, Sharatchandra B. Terra firma-forme dermatosis. Journal of Pakistan Association of Dermatologists. 2015;25(1):52-4.
6. Ratcliffe A, Williamson D, HesselingM. Terra firma-forme dermatosis: it's easy when you know it. Arch Dis Child. 2013;98(7):520.
7. Asslan NC, Guler S, Demirci K, Isiyel E. Features of terra firma-forme dermatosis. Ann Fam Med. 2018;16(1):52-4.
8. Berk DR. Terra firma-forme dermatosis: a retrospective review of 31 patient. Pediatr Dermatol. 2012;29(3):297-300.
9. Browning J, Rosen T. Terra firma-forme dermatosis revisited. Dermatol Online J. 2005;11(2):15.
10. Unal E, Guarneri C, Chokoeva AA, Wollina U, Tchernev G. Terra firma-forme dermatosis. Wien Med Wochenschr. 2017;167(3-4):66-9.
11. Tavli YU, Mevlitoglu I, Toy H, Unal M. Terra firma forme disease. J Paediatr Child Health. 2012;48(11):1046-7.
12. Guarneri C, Guarneri F, Cannavo SP. Terra firma-forme dermatosis. Int J Dermatol. 2008;47(5):482-4.
13. Ashique KT, Kaliyadan F, Goyal T. Terra firma-forme dermatosis: reports of a series of 11 cases and brief review of the literature. Int J Dermatol. 2016;55(7):769-74.
14. Pavlović MD, Dragoš V, Potočnik M, Adamič M. Terra firma-forme dermatosis in a child. Acta Dermatovenerol Alp Pannonica Adriat. 2008;17(1):41-2.
15. Leung AKC. Terra firma-forme dermatosis. J Pediatr. 2018;195:302.
16. Chun SW, Lee SY, Kim JB, Choi HM, Ro BI, Cho HK. A case of terra firma-forme dermatosis treated with salicylic acid alcohol peeling. Ann Dermatol. 2017;29(1):83-5.

Terra firma forme dermatosis – prikaz dva bolesnika i pregled literature

Sažetak

Terra firma forme dermatosis (TFFD) ili Dankanova „prljava" dermatoza je bizarna, stečena idiopatska dermatoza. Karakterišu je žućkaste ili braonkaste lezije, nalik prljavštini, koje se ne mogu ukloniti uobičajenim pranjem vodom i sapunom, ali nestaju nakon trljanja 70% etil alkoholom ili izopropil-alkoholom. Prebrisavanje alkoholom omogućava dijagnozu i istovremeno terapiju ovog oboljenja. Prikazujemo dva dečaka, uzrasta 14 i 11 godina, sa asimptomatskim, braonkastim, prljavštini sličnim lezijama na koži grudnog koša kod prvog i podlaktica kod drugog, koje su bile prisutne duže od mesec dana. Oba pacijenta su održavala redovnu higijenu. Dijagnoza je potvrđena trljanjem kožnih promena 70% etil-alkoholom, nakon čega su promene nestale. TFFD često izaziva zabrinutost kod pacijenata i roditelja obolele dece. Zbog slične kliničke slike sa drugim dermatozama, bolest se može pogrešno dijagnostikovati. Stoga je prepoznavanje TFFD važno za dermatologe i pedijatre, kako bi se pacijentima objasnila benigna priroda oboljenja i izbegla nepotrebna dijagnostička ispitivanja.

Ključne reči: Hiperpigmentacija; Kožne bolesti; Etanol; Dijagnoza; Terapija; Prikazi slučajeva

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DERMOSCOPY OF THE MONTH
Dermoscopic Features of Sebaceous Nevus - a Report of 4 Cases

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Abstract

Sebaceous nevus is a congenital hamartoma commonly associated with the development of secondary neoplasms. It has a predilection for the scalp and less commonly manifests on the face, the neck, and the trunk. The lesions presented in our cases are from the trunk of a 19-year old man, the forehead of a 25-year old man, the scalp of a 22-year old woman and from the face of a 45-year old man. Two of four cases were associated with secondary neoplasms, syringoma and basal cell carcinoma. Dermoscopy of nevus sebaceous demonstrated yellowish-brown globular structures, presenting either singly or in clusters and pink-brown-grey papillary appearance. The specific dermoscopic findings in our case associated with basal cell carcinoma were fine arborizing and serpiginous vessels at the periphery of the lesion and exophytic grey papillary structures. Dermoscopy can be a useful diagnostic tool for diagnosing and monitoring nevus sebaceous in order to detect different tumors associated with nevus sebaceous and avoid unnecessary excisions and scars in aesthetically sensitive locations.

Key words: Skin Neoplasms; Dermoscopy; Nevus; Neoplasms, Second Primary; Nevus, Sebaceous of Jadassohn; Diagnosis

Introduction

Sebaceous nevus is a congenital hamartoma, characterized by hyperplasia of the epidermis, immature hair follicles, and sebaceous and apocrine glands (1, 2).

It may be present at birth or develop in early childhood. It has a predilection for the scalp and less commonly manifests on the face, neck, and trunk. In early childhood, nevus sebaceous presents clinically as a smooth yellowish hairless plaque and during adolescence, lesions acquire a verrucous appearance; in late adulthood, they are commonly associated with the development of secondary neoplasms (1, 2). Different evolutionary stages of nevus sebaceous demonstrate different dermoscopic features. Detecting specific dermoscopic features of nevus sebaceous is especially important for its monitoring in order to detect a malignant transformation (3).

Case Reports

Case 1

A 19-year old man presented to our Department in May 2006 with a verrucous lesion on his left thoracic region. The physical examination revealed a brownish verrucous papule with irregular shape and border (Figure 1). Dermoscopy revealed yellow-grayish papillary appearance on the pink background (Figure 2). The total surgical excision was performed and histologic finding was specific for sebaceous nevus.

Case 2

A 25-year old man presented to our Department in February 2006 with a periorbital verrucous lesion. The physical examination revealed well-circumscribed brown colored, wart-like, irregularly shaped lesion with heterogenous appearance (Figure 3). Dermoscopy showed yellowish-brown globules aggregated

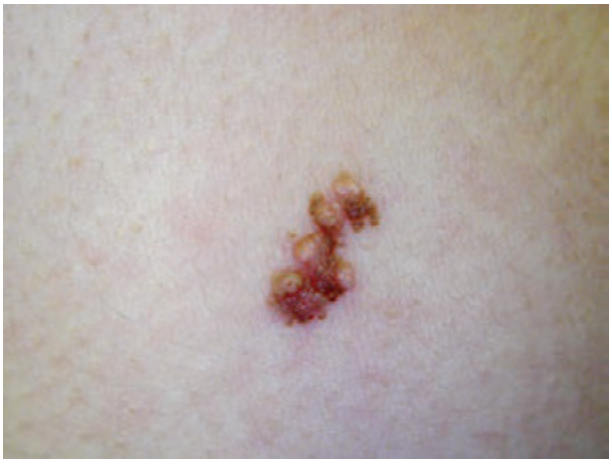

Figure 1. Verrucous brownish papule on the left thoracic region.

in clusters with pink-grey papillary appearance at the periphery of the lesion (Figure 4). The lesion was removed surgically and histopathology revealed nevus sebaceous.

Case 3

The third patient was a 22-year old woman an presenting with a skin colored plaque with central crust on her scalp, which recently changed its appearance. Dermoscopy revealed yellowish-white globules and pink papillary appearance with central erosion (Figure 5). Histopathology revealed inflamed nevus sebaceous and syringoma.

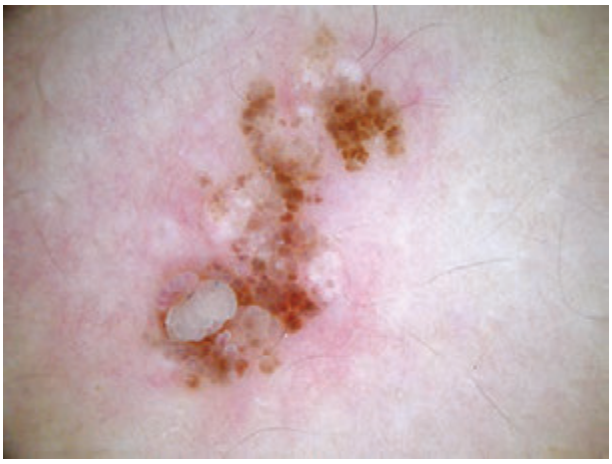

Figure 2. Dermoscopy of the verrucous lesion on the left thoracic region: yellow-grayish papillary appearance on the pink background.

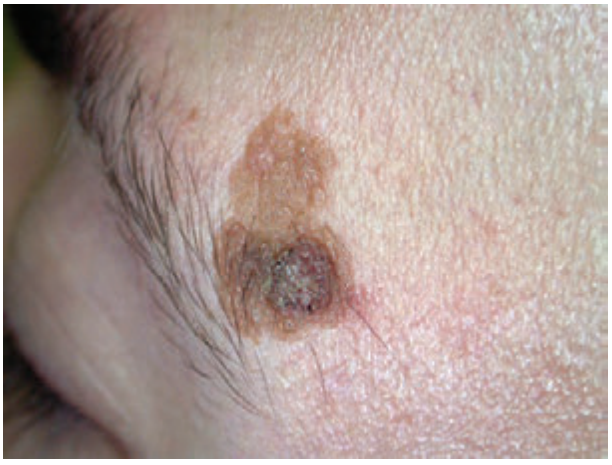

Figure 3. Periorbital verrucous plaque with heterogenous appearance.

Case 4

The fourth patient was a 45-year old man who presented with a painless pink-brown papillomatous plaque on his face. He stated that the lesion had been present since his birth, but recently, some alterations occurred in its shape and size. Dermoscopy showed multicolored brown-pink papillary appearance, pink-grey exophytic papillary structures with yellowish and brown globules organized in clusters, wart-like lesions and peripheral serpiginous and arborescent vascularization (Figure 6). The total surgical excision was performed and histologic finding revealed nevus sebaceous and incipient basal cell carcinoma.

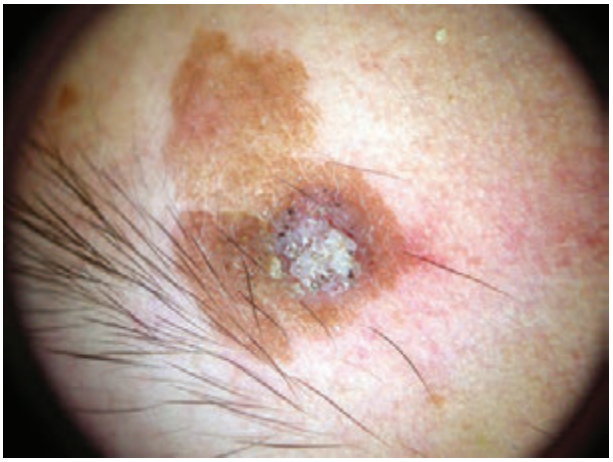

Figure 4. Dermoscopy of the periorbital verrucous lesion: yellowish-brown globules aggregated in clusters with pink-grey papillary appearance at the periphery of the lesion.

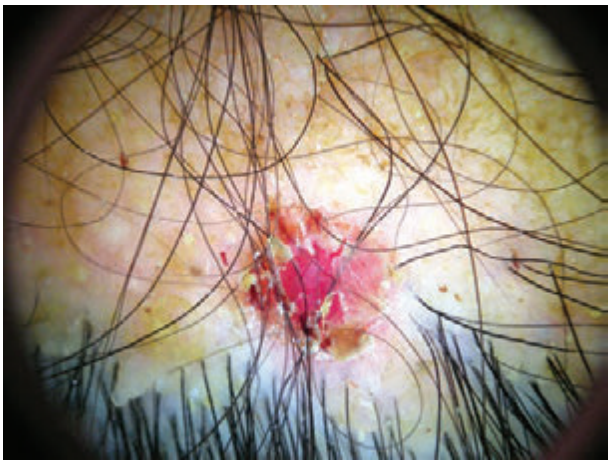

Figure 5. Dermoscopy of the skin colored plaque on the scalp: yellowish-white globules and pink papillary appearance with central erosion.

Discussion

The clinical history of nevus sebaceous may be divided into three evolutionary stages. In early childhood, nevus sebaceous presents clinically as a smooth yellowish hairless plaque. During adolescence, lesions acquire a verrucous appearance and in late adulthood, they are commonly associated with the development of secondary neoplasms. About 10-20% of nevus sebaceous cases are complicated with malignant or benign neoplasms (4-7). For this reason, complete surgical excision is recommended before puberty for treatment of nevus sebaceous (8, 9).

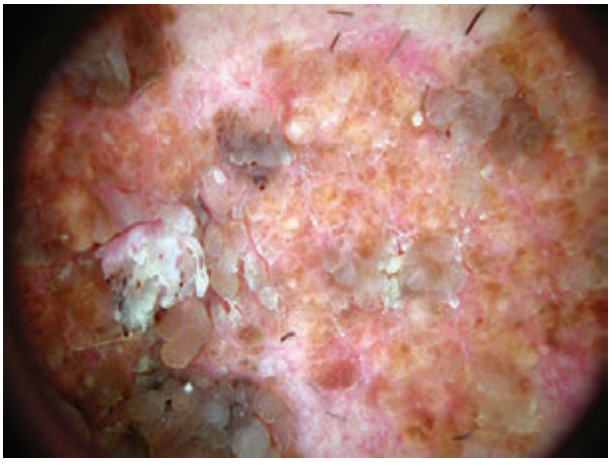

Figure 6. Dermoscopy of the pink-brown papillomatous plaque on the face: multicolored brown-pink papillary appearance, pink-grey exophytic papillary structures with yellowish and brown globules organized in clusters, wart-like lesions and peripheral serpiginous and arborescent vascularization.

On the other hand, nevus sebaceous shows distinctive dermoscopic features, which makes it possible to monitor it and avoid unnecessary excisions and scars on the face and other aesthetically sensitive locations (3). There are only a few case reports describing dermoscopic features of sebaceous nevus. Kelati et al. described different dermoscopic patterns of nevus sebaceous according to its evolutionary stages in the only published study of the dermoscopic features of 13 sebaceous nevi (3).

In the first stage of nevus sebaceous, Kelati et al. noticed yellowish globules aggregated in the clusters on the yellow background, while in the second stage of elevated verrucous plaques, four dermoscopic features were described – whitish-yellow lobular or papillary structures, yellow-grayish papillary appearance, brown globules on the yellow background, and yellowish globules aggregated in clusters, which was the most frequent dermoscopic aspect in the first and the second stages of nevus sebaceous (3). Lesions in our last three cases exhibited yellowish-white-brown globules presented either singly or aggregated in clusters. Yellow-pink-grey papillary appearance was a distinct dermoscopic finding in all our cases .

Dermoscopy is especially useful in detecting tumors associated with nevus sebaceous. The largest study that analyzed dermoscopy of tumors associated with nevus sebaceous was conducted by Zaballos et al. They analyzed dermoscopic features of 58 histopathologically confirmed cases of secondary neoplasms arising in nevus sebaceous (4). The most common reported benign neoplasms associated with nevus sebaceous were trichoblastoma and syringocystadenoma papilliferum and the most common malignant neoplasm was basal cell carcinoma. The most common dermoscopic pattern associated with basal cell carcinoma was the presence of asymmetrical large blue-grey ovoid nests and arborizing vessels, found in 50% of cases (4). Histopathology of our fourth case revealed nevus sebaceous and incipient basal cell carcinoma. The specific dermoscopic findings in this case were fine arborizing and

serpiginous vessels at the periphery of the lesion and exophytic grey papillary structures.

Zaballos et al. concluded that benign adnexal tumors associated with nevus sebaceous usually mimic dermoscopic patterns of basal cell carcinoma (4).

Conclusion

The most specific features of different stages of sebaceous nevus are yellowish or brown globules aggregated in clusters on the yellow background, whitish-yellow lobular or papillary structures, and yellow-grayish papillary appearance. However, larger studies are needed to define specific dermoscopic criteria for diagnosis of nevus sebaceous and its associated tumors.

Dermoscopy can be a useful diagnostic tool for diagnosing and monitoring nevus sebaceous in order to detect different tumors associated with nevus sebaceous and avoid unnecessary excisions and scars in aesthetically sensitive locations.

References

1. Prateek K, Banwarilal MR, Garg M, Chaudhary SS. Nevus sebaceous of Jadassohn - a rare case report. IOSR Journal of Dental and Medical Sciences. 2016;15(12):58-60.
2. Gupta SK, Gupta V. Basal cell carcinoma and syringocystadenoma papilliferum arising in nevus sebaceous on face - a rare entity. Indian J Dermatol. 2015;60(6):637.
3. Kelati A, Baybay H, Gallouj S, Mernissi FZ. Dermoscopic analysis of nevus sebaceus of Jadassohn: a study of 13 cases. Skin Appendage Disord. 2017;3(2):83-91.
4. Zaballos P, Serrano P, Flores G, Bañuls J, Thomas L, Llambrich A, et al. Dermoscopy of tumours arising in naevus sebaceous: a morphological study of 58 cases. J Eur Acad Dermatol Venereol. 2015;29(11):2231-7.
5. Cribier B, Scrivener Y, Grosshans E. Tumors arising in nevus sebaceus: a study of 596 cases. J Am Acad Dermatol. 2000;42(2 Pt 1):263-8.
6. Idriss MH, Elston DM. Secondary neoplasms associated with nevus sebaceus of Jadassohn: a study of 707 cases. J Am Acad Dermatol. 2014;70(2):332-7.
7. Rosen H, Schmidt B, Lam HP, Meara JG, Labow BI. Management of nevus sebaceous and the risk of Basal cell carcinoma: an 18-year review. Pediatr Dermatol. 2009;26(6):676-81.
8. Santibanez-Gallerani A, Marshall D, Duarte AM, Melnick SJ, Thaller S. Should nevus sebaceus of Jadassohn in children be excised? A study of 757 cases, and literature review. J Craniofac Surg. 2003;14(5):658-60.
9. Barkham MC, White N, Brundler MA, Richard B, Moss C. Should naevus sebaceus be excised prophylactically? A clinical audit. J Plast Reconstr Aesthet Surg. 2007;60(11):1269-70.

Dermoskopske karakteristike sebacealnog nevusa – prikaz četiri slučaja

Sažetak

Uvod. Sebacealni nevus predstavlja kongenitalni hamartom koji je često udružen sa razvojem sekundarnih neoplazmi. Može biti prisutan na rođenju ili se javlja tokom ranog detinjstva. Najčešće se nalazi na poglavini, vratu i trupu. Sebacealni nevus obično ima tri evolutivna klinička stadijuma. Različiti evolutivni stadijumi sebacealnog nevusa pokazuju različite dermoskopske karakteristike. Zbog udruženosti sebacealnog nevusa sa različitim benignim i malignim kutanim tumorima, indikovana je ekscizija ovih promena pre puberteta. **Prikazi slučaja.** Prikazujemo četiri slučaja: 19-godišnji muškarac sa verukoznom lezijom na grudnom košu, muškarac od 25 godina sa periorbitalnom verukoznom lezijom, žena od 22 godine sa plakom u boji kože na poglavini i muškarac starosti 45 godina sa papilomatoznim plakom na licu. Pacijenti su ambulantno pregledani na Klinici za dermatovenerologiju VMA tokom 2006. i 2007. godine. Učinjena je dermoskopija svih opisanih promena, kao i ekscizija opisanih promena i uzorci su poslati na patohistološku analizu. Patohistološki nalazi svih opisanih promena su odgovarali sebacealnom nevusu, a u trećem i četvrtom slučaju sebacealnom nevusu i cilindomu i sebacealnom nevusu i bazocelularnom karcinomu. **Diskusija.** Klinička slika sebacealnog nevusa može biti podeljena u tri različita evolutivna stadijuma. U jedinoj do sada objavljenoj studiji koja se bavila dermoskopskim karakteristikama sebacealnog nevusa (*Kelati et al*.), opisani su različiti dermoskopski obrasci evolutivnih stadijuma sebacealnog nevusa. Takođe, u studiji koja se bavila dermoskopskim obrascima sekundarnih neoplazmi koje se javljaju udružene sa sebacealnim nevusom (*Zaballos et al*.), opisane su dermoskopske karakteristike koje su specifične za najčešće benigne i maligne tumore koji se javljaju udruženo sa sebacealnim nevusom. **Zaključak.** Žute ili smeđe globule raspoređene u ni-

zovima, na žutoj podlozi, beložute papilarne ili lobularne strukture i žutosivi papilarni izgled su najčešće dermoskopske karakteristike sebacealnog nevusa. Neophodne su veće studije koje bi utvrdile jasne dermoskopske kriterijume za prepoznavanje sebacealnih nevusa, kao i sebacealnih nevusa i sa njima udruženih neoplazmi, što bi omogućilo njihovo lakše praćenje i izbegavanje nepotrebnih ekscizija.

Ključne reči: Kožne neoplazme; Dermoskopija; Nevus; Drugi primarni tumori; Jadason nevus lojne žlezde; Dijagnoza

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A Report on the 14th Congress of the European Association of Dermato-Oncology

The 14th Congress of the European Association of Dermato-Oncology (EADO) was held from 6-9 November 2018 at the Palau de Congressos de Catalunya venue in Barcelona, Spain. Prof. Joseph Malvehy and Prof. Claus Garbe were the Congress presidents.

This congress has already become a major interdisciplinary meeting for clinicians and basic scientists working in the challenging fields of melanoma and non-melanoma skin cancers. Also, the EADO Congress is a unique opportunity to attend lectures provided by worldwide recognized experts in the field of melanoma and skin cancers. The 4-day rich scientific program covered all aspects of melanoma and skin cancers, from epidemiology, diagnosis and prevention to the results of the latest clinical trials in dermato-oncology. The program combined research and new clinical data which were presented at the plenary sessions; keynote lectures and symposia together with breakout sessions for the discussion of crucial aspects of the organization of skin cancer/melanoma centers, access of patients to specific drugs, collaboration with patients' associations and experiences in different health scenarios in all regions of the world. Around 10,000 participants were registered for the event, with scientific program that consisted of 4 parallel sessions with over 100 oral presentations and 166 poster presentations. The entire scientific content including the presentation slides is available at EADO web-site for members (more information at www.eado.org).

Prof. Lidija Kandolf Sekulović was a chairperson with Prof. Peter Mohr in the session "Course in dermato-oncology for nurses" as well as in the sessions "Difficult to treat subtypes of melanoma" with prof. Cristina Carrera and "Equitance & access to treatments in Europe" with Prof. Anna-Maria Forsea, during which she had presentations on systemic treatments of melanoma, mucosal melanoma, access to treatments for skin cancer and melanoma registries. During the Breakout session, which was co-chaired with Prof. Jeffrey E. Gershenwald and Prof. Luc Thomas, she presented the results of the European study named "Access to innovative medicines for metastatic melanoma and non-melanoma skin cancer in Europe and worldwide - update 2017".

The next 15th EADO Congress will take place at the Maison de la Chimie in Paris, France, from 24-27 April, 2019.

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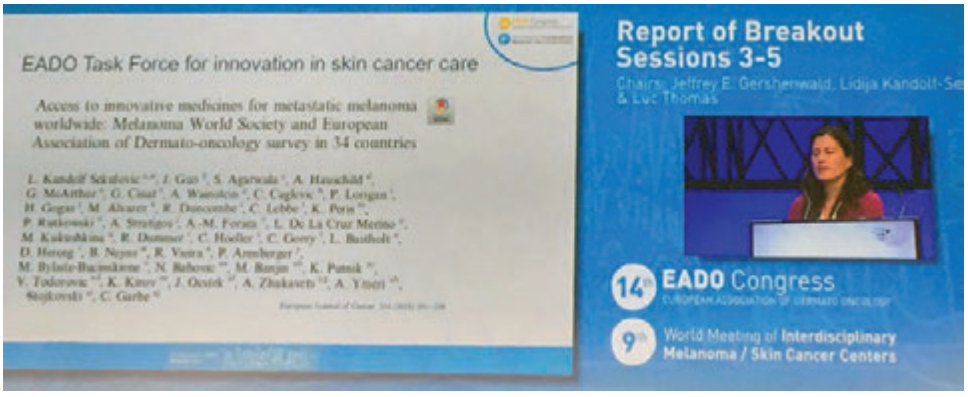

A Report on the 27th Congress of the European Academy of Dermatology and Venereology in Paris, France

Around 7500 participants gathered at the „Palais des Congrès de Paris" from 12th to 17th of September, 2018 to attend the 27th EADV Congress. Paris is one of the major European Centers for Dermatologists from all over the world, besides being the most "Culturally Vibrant City" in the EU, as ranked by European Commission in 2017.

In a freshly-structured thematic session format with various tracks, the Congress was designed to meet various expectations of the participants, with many opportunities to further develop skills and continue their medical education. Sessions of different formats covered the important fields in dermatology and venereology. The intensive 4-day programme included more than 150 stimulating sessions, arranged in the successful track system, from contributors originating from more than 50 countries worldwide.

Almost 750 speakers from over a hundred countries were welcomed. The programme included plenary lectures, educational classes (mostly focused towards residents), review and update sessions (directed at specialist dermato-venereologists), expert council and discussions (for expert groups) what's new, spotlights, clinical cases and free communications of selected abstracts.

The scientific programme was complemented by keynote lectures from distinguished experts on the following topics: Vasculitis and vasculopathies, Can we cure metastatic melanoma? Development of HIV therapies, Skin microbiome in health and disease, Skin infection and atopic dermatitis, Congenital naevi: Diagnosis, spectrum and therapy and Skin fragility syndromes.

This year's focus was on Clinical Oncology and two full day tracks covered topics such as genetic predisposition, genetic causes and the environment, targeting the tumour environment, melanoma, lymphomas, non-melanoma skin cancer, rare skin tumours, as well as adverse effects of chemotherapies and targeted therapies. Popular highlights included also the Spotlights sessions, the Late-breaking News summarizing the most

Figure 1. Danica Tiodorović, Ketty Perris, Lidija Kandolf Sekuović and Željko Mijušković (from left to right) at the promotional cockatil for the World Congress of Dermatology

recent, important studies published to date, and selection of practical "hands-on" workshops. Another exceptional programme was Aesthestic Sunday, showing improvement in cosmetic and aesthetic dermatology.

The participation of Serbian dermatologists was well appreciated, because many of them had presentations: 33 e-posters in 21 submission topics. Also, two lectures were delivered, by prof. Miloš Nikolić ("Clinical and pathological spectrum of SCLE and SLE") and by Dr Jovan Lalošević ("Androgenetic alopecia in men").

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Figure 2. At the President's Dinner: Lidija Kandolf Sekulović, Željko Mijušković, Asja Prohić, Mateja Dolenjc-Vojč, Miloš Nikolić, Branka Bonači Nikolić (from left to right)

FORTHCOMING EVENTS

Dermatology and Venereology Events 2018

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
12-16 September, 2018	27th EADV Congress, Paris France	13 March, 2018	www.eadvparis2018.org
05-06 October, 2018	Pediatric Dermatology, Specialist Course, Lausanne, Switzerland	13 March, 2018	www.eadv.org
4-6 October, 2018	ESTRO School, Multidisciplinary management of non- melanoma skin cancer, Brussels, Belgium		www.estro.org
11-13 October, 2018	22ndBDD, Belgrade, Serbia	1 June, 2018	www.udvs. org
29-30 October, 2018	6th International Conference on HIV/AIDS, STDs and STIs, San Francisco, USA		www.hiv-aids-std.conferenceseries.com
6-9 November, 2018	14th Congress of the EADO, Barcelona, Spain	10 September, 2018	www.congresseado-melanomacenters2018.com
9-11 November, 2018	EADV Course- Skin Cancer, Trieste, Italy		www.eadv.org
14-17 November, 2018	CILAD 2018, Sao Paulo, Brazil	10 September, 2018	www.cilad2018.com
5-6 December, 2018	GA2LEN Global Urticaria Forum (GUF 2018), Berlin, Germany	10 September, 2018	www.globalurticariaforum.org

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AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists*. The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

Categories of Manuscripts

1. Editorials (limited to 5 pages) generally provide commentary and analyses concerning topics of current interest in the field of dermatology and venereology. Editorials are commonly written by one author, by invitation.

2. Original studies (limited to 12 pages) should contain innovative research, supported by randomized trials, diagnostic tests, outcome studies, cost-effectiveness analysis and surveys with high response rate.

3. Review articles (limited to 10 pages) should provide systemic critical assessment ofliterature and other data sources.

4. Professional articles (limited to 8 pages) should provide a link between the theory and practice, as well as detailed discussion or medical research and practice.

5. Case reports (limited to 6 pages) should be new, interesting and rare cases with clinical significance.

6. History of medicine (limited to 10 pages) articles should be concerned with all aspects of health, illness and medical treatment in the past.

7. Short Communications (limited to 3 pages) should disseminate most current results and developments in the shortest possible time. They will be reviewed by expert reviewers and evaluated by the Editor.

The journal also publishes book reviews, congress reports, as well as reports on local and international activities, editorial board announcements, letters to the editor, novelties in medicine, questions and answers, and “In Memoriam”. All submitted manuscripts will undergo review by the editor-in-chief, blind review by members of the manuscript review panel or members of the Editorial Board. Manuscripts submitted to this journal must not be under simultaneous consideration by any other publisher. Any materials submitted will NOT BE RETURNED to the author/s.

All manuscripts are to be submitted to the **Editor in Chief: Prof. Dr. Lidija Kandolf Sekulović,** Clinic of Dermatovenereology, School of Medicine, Military Medical Academy, Crnotravska 17, Belgrade, Republic of Serbia, by mail to: serbjdermatol@gmail.com

Manuscripts for submission must be prepared according to the guidelines adopted by the International Committee of Medical Journal Editors (www.icmje. org). Please consult the latest version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

1. Manuscript Preparation Guidelines

The manuscript should be written in English, typed in double spacing throughout on A4 paper, on one side only; Use Times New Roman, font size 12, with 30 lines and 60 characters per line. Articles must be written clearly, concisely and in correct English. Accepted manuscripts in need of editing will be returned after editing to the corresponding author for approval. When preparing their manuscripts, authors should follow the instructions given in the *Categories of Manuscript:* the number of pages is limited (including tables, figures, graphs, pictures and so on to 4 (four)), and all the pages must be numbered at the bottom center of the page.

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

– The title ofthe article, which shouldbe informative, without abbreviations and as short as possible;

– A running title (limited to 30 characters);

– Authors’ names and institutional affiliations;

– The name, mailing address, telephone and fax numbers, and email of the corresponding author responsible for correspondence about the manuscript. Furthermore, authors may use a footnote for acknowledgements, information and so on.

1.2. Abstracts

A structured abstract in English (limited to 150 words) should follow the title page. The abstract should provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors sho uld avoid using abbreviations.

– An **abstract in Serbian language,** (limited to 150 words) should follow the second page. It should contain a briefing on the purpose of the study, methods, results and conclusions, and should not contain abbreviations.

1.3. A list of abbreviations

Use only standard abbreviations, because use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units — SI, available at *http:// w*ww.bipm.fr/en/si/.

1.4. Cover Letter

Manuscripts must be accompanied by a cover letter, which should include a date of submission, statement that the manuscript has been read and approved by all the authors and that the authorship requirements have been met. It should also include the name, address, and telephone number of the corresponding author, who is responsible for communicating with other authors about revisions and final approval of the proofs. The original copy of the cover letter, signed by all authors, should be enclosed with the manuscript.

2. Tables and illustrations

Tables should capture information concisely

and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.

– Submit tables in separate files, not included in the manuscript. Tables are to be double spaced and numbered sequentially, with Arabic numbers (Table 1, Table 2, etc.), in order of text citation. Each column, including the first, must have a heading. Provide a brief title for each table. Put all explanatory matter in footnotes, including any nonstandard abbreviations used in the table.

– Figures should be submitted in a separate file, not included in the manuscript document. Cite figures consecutively, as they appear in the text, with Arabic numbers (Fig. 1, Fig. 2, Fig. 3, etc.). Each figure must be assigned a title, as well as a legend. Legends should appear on a separate page, not with each figure. The Legend Page is to be numbered in sequence after the last page of the references list. Figures should be professionally drawn, as sharp black-and-white or color photographs. If photographs of persons are used, either the subjects must not be identifiable, or their pictures must be accompanied by written permission to use them.

3. References

References in the text, tables and legends should be identified by Arabic numerals in parentheses. Number references consecutively in the order in which they are first mentioned in the text. The Vancouver System of referencing should be used. List each author's last name and initials; full first names are not included. List all authors, but if the number exceeds six, give the first six followed by „et al." National journals, which are not indexed in Index Medicus, should be abbreviated according to the style in the List of Abbreviated Titles of Yugoslav Serial Publications available on http:// vbsw.vbs.rs. For further information please visit www. ICMJE.org.

4. Author's Statements

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To ensure fair and objective decision-making, authors must declare any associations that pose a conflict of interest (financial, personal or professional) in connection with evaluated manuscripts. If there are no conflicts of interest, the following statement should be included *before the References* (or at the end of the *Acknowledgments sectio*n):

Conflict of interest: Authors state no conflict of interest.

– Informed Consent

The protection of privacy is a legal right that must not be breached without individual informed consent. In cases where the identification of personal information is necessary for scientific reasons, authors should obtain full documentation of informed consent, including written permission from the patient prior to inclusion in the study.

The following (or similar) statement should be included *in the Methods section*:

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– Authorization for the use of human subjects

Manuscripts containing information related to human use should clearly state that the research has complied with all relevant national regulations and institutional policies and has been approved by the authors' institutional review board or equivalent committee. Copies of the guidelines and policy statements must be available for review by the Managing Editor if necessary. The editors reserve the right to seek additional information or guidance from reviewers on any cases in which concerns arise. All investigation with human subjects must have been conducted by following the tenets of the Helsinki Declaration, what is more authors must identify the committee or review board approving the experiments, and provide a statement indicating approval of the research. The following (or similar) statement should be included *in the Methods section*:

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If the manuscript does not contain any study that requires human or animal ethical approval, the following statement should be included in the *Methods section*:

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5. Additional Information

Accepted manuscripts are edited and returned to the corresponding author for proof. Then a final version of the manuscript will be requested in a defined period of time. Authors will be notified of acceptance or rejection by email, within approximately 4 weeks after submission.

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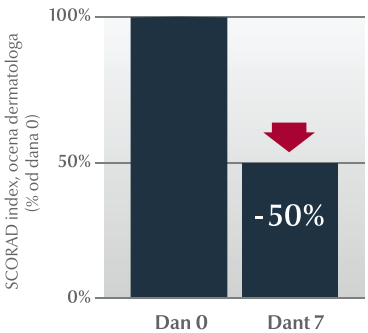

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