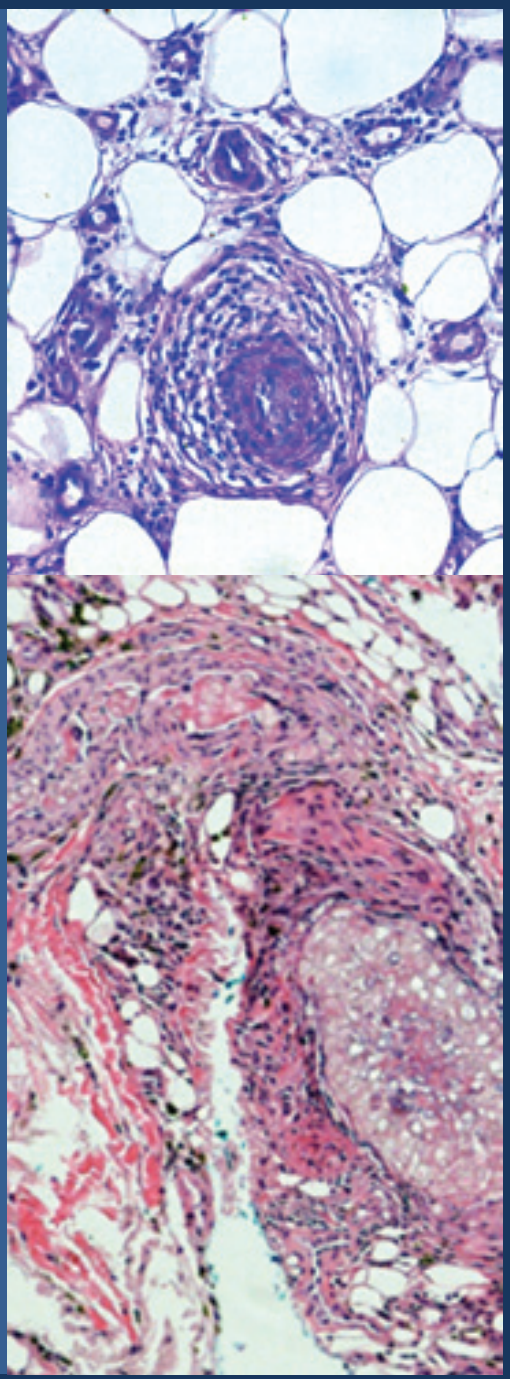
SERBIAN JOURNAL OF
Dermatology and Venereology

ISSN 1821-0902 ISSN 2406-0631 UDC 616.5(497.11) Volume 10, Number 2, June 2018



Published by the
Serbian Association of Dermatovenereologists

SJDV

The Journal is published four times a year with the circulation of 360. Manuscripts are to be submitted to the Editor-in-Chief: Prof. Dr. Lidija Kandolf Sekulović, Vojnomedicinska akademija, Klinika za kožne i polne bolesti, 11000 Beograd, Crnotravska 17
E-mail: serbjdermatol@gmail.com, Tel: +381 11 266 11 22; +381 11 266 00 20.
Open access: www.udvs.org

Published on behalf of The Serbian Association of Dermatovenereologists by Zlatni presek, Beograd

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Serbian Journal of Dermatology and Venereology 2018; 10 (2):35-68.

DOI: 10.2478/sjdv-2018-0006

Lichen Planus and Hepatitis C Virus Infection: A clinical Evaluation of 168 Cases

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UDC 616.516:616.36-002

Abstract

Introduction. Hepatitis C virus (HCV) infection is one of the factors which can lead to a chronic liver disease and hepatocellular carcinoma. There have been several reports on the association of oral lichen planus with hepatic disorders, i.e. hepatitis C infection in particular. Considering the controversies about the association of lichen planus with HCV infection on one hand and considerable impact of hepatitis C on the occurrence of chronic liver disease on the other hand, we investigated the association between lichen planus and HCV infection in Sanandaj City. **Methods.** This cross sectional study included 168 patients with lichen planus, who were referred to the Dermatology Clinic of Besat Hospital between 2014 and 2016. The diagnosis of lichen planus was made by our dermatologist and HCV antibody titer was determined for every patient. **Results**. Mean age of the patients was 39.7±13.3 years and mean duration of the disease was 14.8 months. 107 (63.7%) patients were men. The highest frequency of lichen planus was recorded in the housewives (30.4%). In 52 (31%) patients the genital area was involved and it was the most common site. In 6 (3.6%) patients the oral mucosa was involved and it was the least common site in our study. Only 4 (2.7%) patients had family history of lichen planus. None of 168 patients included in this study was found to have HCV infection. **Conclusion.** In this study, we found no relationship between lichen planus and HCV infection. Yet, the exact mechanism underlying the occurrence of lichen planus in the patients with HCV infection has not been determined. Therefore more studies on this subject are recommended.

Key words: Lichen Planus; Hepatitis C; Hepacivirus; Diagnosis; Cross-Sectional Studies; Comorbidity

Introduction

Hepatitis C virus infection is one of the factors which can result in a chronic liver disease and hepatocellular carcinoma. The main way of transmission is through transfusion of blood and its products (1). Hepatitis C virus infection can lead not only to hepatic disorders but also to extrahepatic manifestations such as lichen planus, cryoglobulinemia, membranous glomerulonephritis, Sjogren's syndrome, rheumatoid arthritis (2). In general hepatitis C can be associated with autoimmune disorders. The question concerning the association between hepatitis C infection and oral lichen planus has been discussed for a long time (3, 4). Lichen planus is an inflammatory disorder with distinct clinical and pathological findings which can involve skin, mucous membranes, nail and hair follicles (5). Different types of lichen planus including annular, atrophic, follicular, hypertrophic and linear ones have been indentified (6). Lichen planus is considered to be an immunologically mediated disorder and cellular immunity has an essential role in the occurrence of clinical manifestations of lichen planus (7). The first case of lichen planus in a patient with hepatitis C was diagnosed in France and the diagnosis was confirmed by histopathological examination of a skin biopsy (5). Many studies have been carried out in different parts of the world and different results have been obtained about the association of lichen planus with hepatitis C and B infections (8-11).

Table 1. Frequency rate of lichen planus in Sanandaj City

Variables		Number	Percentage
Gender	Male	107	63.7
	Female	61	36.3
Occupation	Worker	19	11.3
	Civil servant	30	17.9
	House-wife	51	30.4
	Farmer	10	10
	Self-employed	6	3.6
	High school and university students	12	7.1
	Unemployed	6	3.6
	Others	28	16.7
Site of lesions	Genital area	52	31
	Forearm, hand, arm	33	19.6
	Leg and thigh	41	24.4
	Abdomen, chest, back	21	12.5
	Oral mucosa	6	3.6
	Scalp	7	4.2
	Generalized	8	4.8
Family history	Positive	4	2.7
	Negative	164	97.3
History of other diseases	Positive	48	28.5
	Negative	120	71.5
History of use of medications	Positive	40	25
	Negative	126	75
Stress	Positive	53	31.5
	Negative	115	68.5
Total	-	168	100

Considering different results of the studies on the association of lichen planus with hepatitis C and considerable impact of hepatitis C on the occurrence of chronic liver disease, we investigated the association between lichen planus and hepatitis C infection in Sanandaj City.

Methods

This cross sectional study included 168 patients who were referred to the Dermatology Clinic of Besat Hospital in Sanandaj City between 2014 and 2016. Demographic data of the patients including age, gender, occupation and place of residence were recorded. The authors claim to have obtained all ap-

propriate consent forms from the patients. The patients understood that their names and initials would not be published and due efforts would be made to conceal their identity (IR.MUK.REC.1397.5002). We also recorded the site of lesions, history of use of medications, and family history of lichen planus for every patient. Diagnosis of lichen planus was made by our dermatologist on the basis of clinical manifestations. In case of doubt, we took biopsy for histopathological examination. All the patients were tested for HCV antibody. We used Stata12 software for data analysis.

Results

Mean age of the patients was 39.7±13.3 years and mean duration of the disease was 14.8 months. A hundred and seven (63.7%) patients were men. The highest frequency of lichen planus was recorded in the housewives (30.4%), and then in civil servants (17.9). In 52 (31%) patients the genital area was involved and it was the most common site. In 6 (3.6%) patients the oral mucosa was involved and it was the least common site. We found history of other diseases and use of medications in 28.5% and 25% of the patients, respectively. Only 4 (2.7%) patients had positive family history of lichen planus. We did not find any positive HCV antibody test in our study (Table 1). There was a significant difference between the location of the lesions of lichen planus and gender of the patients (P<0.001). However, the site of lesions had no significant statistical relationship with age, duration of lichen planus and history of any other disease (P>0.05) (Table 2).

Discussion

In this study 107 (63.7%) patients were men and the highest frequencies of lichen planus was observed in the housewives (30.4%) and civil servants (17.9%). Prabhu's study included 48 women (73.4%), 15 men (25.3%) and 2 patients below the age of 12 years (12). A study performed by Gimenez (13) included 57 women (56.4%) and 44 men (43.5%). Neither of them is comparable with our study regarding the gender ratio.

According to the results of our study in 52 (31%) patient the genital area was involved and it was the most common site. The oral mucosa was found to be involved in 6 (3.6%) patients and it was the least common site involved by lichen planus. In a study performed by Kavoosi, the skin was involved in 45.1% of the patients, and the skin and mucous membrane were involved in 40.3% of the patients (7). In a Rabiei's study the most common sites involved by lichen planus lesions were the buccal mucosa and lower lip (14).

In another study conducted by Esfandiarpour the oral and gential mucosa were the most common sites involved by lichen planus (67.5%) and classic skin lesions were found in 65% of the patients (15). In one study performed in Italy, keratotic and reticular lichen planus were the most common variants and

Table 2. Frequency rates of the sites of skin lesions in relation to age, duration of disease, gender and history of other disease

Site of lesions Variables	Genital area	Forearm hand, arm	Leg, thigh	Abdomen, chest, back	Oral mucosa	Scalp	Generalized	P-value
Age (years)	37.5±11.1	42.8±14.5	41.9±14.3	39.3±15.1	34.3±14	40.1±10.5	35±11.9	0.398
Duration of disease (month)	12.9±15.1	11.7±20.2	22.1±34.4	10.6±14.7	5.6±3.7	27.7±36.5	9.4±15.9	0.171
Gender								<0.001
Male	49 (45.8)	14 (13.1)	24 (22.4)	8 (7.5)	3 (2.8)	5 (4.7)	4 (3.7)	
Female	3 (4.9)	19 (31.1)	17 (27.9)	13 (21.3)	3 (4.9)	2 (3.3)	4 (6.6)	
History of any other disease								0.754
Positive	12 (25)	12 (25)	14 (19.2)	5 (10.4)	2 (4.2)	2 (2.1)	2 (4.2)	
Negative	40 (33.3)	21 (17.5)	27 (22.5)	16 (13.3)	4 (3.3)	6 (5)	6 (5)	

the most common site of involvement was the buccal mucosa (16). In some studies the most common sites involved by lichen planus were the buccal mucosa and gums followed by the lips (17-19). In one study 16% of the patients with skin lesions of lichen planus and 30% of the patients with mucosal lichen planus had positive HCV antibody tests (20).

In our study none of the patients had positive HCV antibody tests. Parabhu included 65 patients in one study and Boker recruited 48 patients with lichen planus in another study. The results of these studies revealed negative HCV antibody tests which were compatible with the findings of our study (12, 21).

Out of 57 patients with oral lichen planus included in the study performed by Daramola and his colleagues in Nigeria, 9 patients were found to have positive HCV antibody tests while all of the participants in their control group had negative HCV antibody tests (22). Klanrit and his colleagues tested 60 patients with oral lichen planus, for HCV antibody and found 5 (8.23%) patients with positive HCV antibody tests. However, none of the subjects in their control group had positive HCV antibody tests (23). In one study performed by Luis, 2.77% of the patients with oral lichen planus had HCV infection (24). Another study showed a significant relationship between lichen planus and HCV infection (25, 26). Lichen planus is an autoimmune disease. Controversies over the results of different studies on the association between lichen planus and HCV infection may be related to variations in immune response of the individuals and also different genotypes of hepatitis C virus in different parts of the world (27).

Conclusion

In our study we found no relationship between lichen planus and HCV infection. Yet, the exact mechanism underlying the occurrence of lichen planus in the patients with hepatitis C infection has not been understood. Therefore, further studies on this subject are recommended. Early diagnosis of hepatitis C can lead to effective control and treatment of this disease. Therefore determination of HCV antibody titer in the patients with mucosal or skin manifestations of lichen planus may be useful for early diagnosis of HCV infection.

Acknowledgement

The authors gratefully acknowledge the assistance staff of Health Deputy Department and Noor Pathobiology Laboratory. It was funded by the Kurdistan University of Medical Sciences, Sanandaj, Iran

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Lihen planus i virusna infekcija hepatitisom C – klinička procena 168 slučajeva

Sažetak

Uvod. Infekcija virusom hepatitisa C je jedan od faktora koji mogu da dovedu do hronične bolesti jetre i hepatocelularnog karcinoma. Postoji nekoliko radova o vezi između oralnog lihena planus sa poremećajima jetre, pogotovo infekcijom virusom hepatitisa C. Uzimajući u obzir kontroverze o vezi između lihena planus i infekcije virusom hepatitisa C, s jedne strane, i značajnog uticaja hepatitisa C na pojavu hroničnog oboljenja jetre, s druge strane, mi smo ispitivali vezu između lihena planus i infekcije virusom hepatitisa C u gradu Sanandaj. **Metode**. Ova studija poprečnog preseka obuhvatila je 168 pacijenata sa lihenom planus koji su upućeni na Dermatološku kliniku Besat bolnice između 2014. i 2016. godine. Dijagnozu lihena planus postavio je naš dermatolog i titar antitela na virus hepatitisa C određen je za svakog pacijenta. **Rezultati.** Prosečna starost naših pacijenata bila je 39,7 ± 13,3 a prosečno trajanje bolesti bilo je 14,8 meseci. Među pacijentima, muškaraca je bilo 107 (63,7%). Najviša frekvencija lihena planus zabeležena je kod domaćica (30,4%). Kod 52 pacijenta (31%) bila je obuhvaćena genitalna regija – to je i bilo najčešće mesto. Kod šest (3,6%) pacijenata bila je obuhvaćena oralna mukoza – to je bilo najređe mesto u našoj studiji. Samo četvoro pacijenta (2,7%) imalo je porodičnu anamnezu lihena planus. Od 168 pacijenata obuhvaćenih ovom studijom, ni kod jednog nije nađena HCV infekcija. **Zaključak.** U ovoj studiji mi nismo pronašli povezanost između lihena planus i infekcije virusom hepatitisa C. Ipak, tačan mehanizam koji je u osnovi pojave lihena planus kod pacijenata sa infekcijom virusom hepatitisa C nije ustanovljen. Stoga se preporučuje dalje proučavanje ovog problema.

Ključne reči: Lihen planus; Hepatitis C; Hepacivirus; Dijagnoza; Studije preseka; Komorbiditet

Received 28 August, 2018
Accepted 8 September, 2018

DOI: 10.2478/sjdv-2018-0007

Disseminated Fusarium Infections in Acute Lymphoblastic Leukemia

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UDC 616.992:616.155.392

Abstract

Fusarium is a ubiquitous fungal species found in soil and water. While fusarium can cause localized infection in healthy individuals, it most commonly affects those with compromised immune systems, particularly those with prolonged neutropenia. The morality rate of systemic infection approaches one-hundred percent. Here we present two cases of disseminated fusarium infection in two patients with acute lymphoblastic leukemia (ALL) along with review of literatures regarding prophylaxis and treatment.

Key words: Precursor Cell Lymphoblastic Leukemia-Lymphoma; Fusariosis; Case Reports; Immunocompromised Host

Case Report

Patient A was a 45-year-old Caucasian woman with a history of ALL, 182 days status post stem cell transplant, complicated by graft vs. host disease (GVHD) and two relapses of her ALL who presented as an urgent consult to dermatology clinic for a one-week history of rash. Her chemotherapy regimen included an experimental selective tyrosine kinase inhibitor, vincristine, intra-thecal cytarabine, and dexamethasone. Antimicrobial prophylaxis included levofloxacin, acyclovir, and posaconazole. On exam, she had multiple erythematous to purpuric slightly indurated papules and plaques scattered on her face, arms, and legs, along with several tender papules and nodules with occasional dusky centers on the lower legs (Figure 1).

Patient B was also a 45-year-old Caucasian woman with a history of ALL, 225 days status post stem cell transplant, and previous breast cancer who developed a rash two days after being admitted for headache and syncope. Her chemotherapy regimen included a SYK inhibitor and ruxolitinib. Her antimicrobial prophylaxis regimen consisted of acyclo-

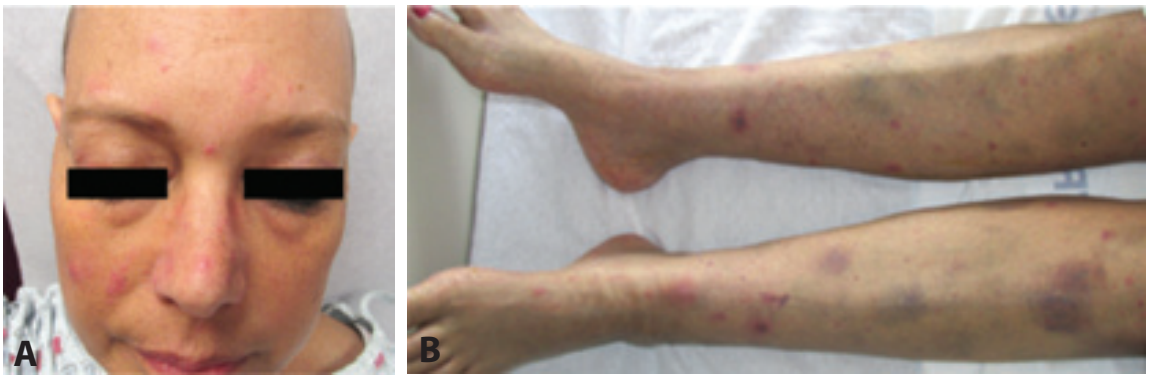

Figure 1. Multiple erythematous to purpuric papules and plaques scattered on her face (A), and legs in Patient A (B)

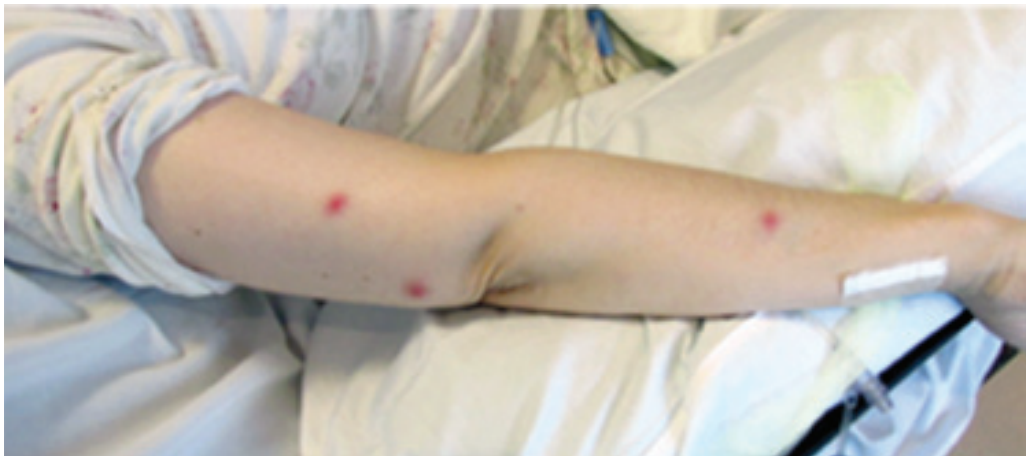

Figure 2. Firm, red, and indurated lesions on her right upper arm in patient B

vir and micafungin. On exam, there were firm, tender, red, and indurated lesions on her right upper arm, anterior neck, and the dorsum of the right foot (Figure 2).

Punch biopsies of the skin and blood cultures were taken from both patients. Hematoxylin-and-eosin, Periodic acid–Schiff (PAS) and Gomori methenamine silver (GMS) stains performed on the skin biopsies showed hyphal elements (Figures 3 and 4) within the blood vessels walls and lumens in both cases. Blood cultures later grew Fusarium, confirming the diagnosis of disseminated *Fusarium* infection in both patients.

Both patients received the standard treatment consisting of IV amphotericin B. Invasive fungal sinusitis was also confirmed in both women via endoscopic debridement of nasopharyngeal mucosa by otolaryngology. Chemotherapy was discontinued in patient A, and Patient B was given G-CSF. Unfortunately, neither patient improved with treatment. Patient A discontinued antifungal treatment and was discharged to home hospice care where she later passed away. Patient B was transferred to the intensive care unit where she eventually succumbed to infection and multiorgan failure.

Discussion

The ubiquitous mold *Fusarium* enters the body via inhalation into the upper airways and lungs as well as through breaks in the skin

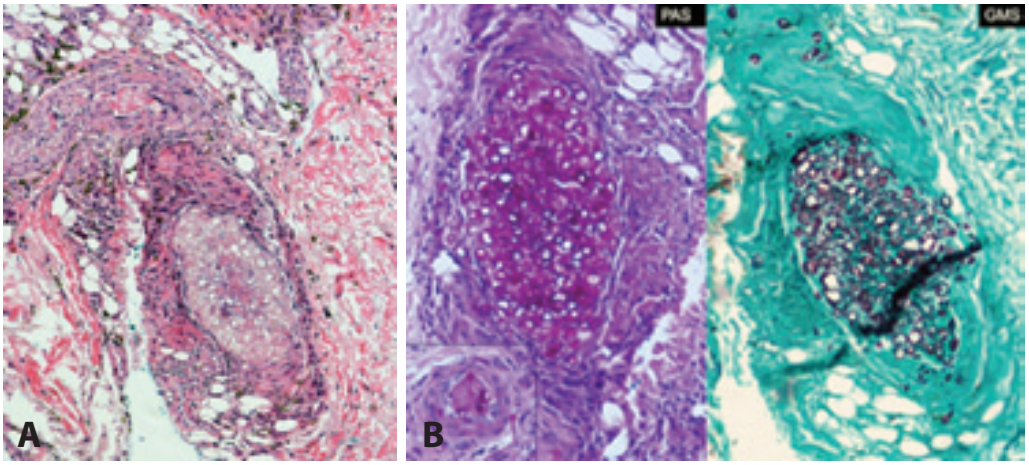

Figure 3. Biopsy from patient A. Cross-sections of numerous hyphal elements occluding blood vessel lumina (A). These fungal elements were also positive on Periodic acid-Schiff (PAS) and Grocott's methenamine silver (GMS) stains (B).

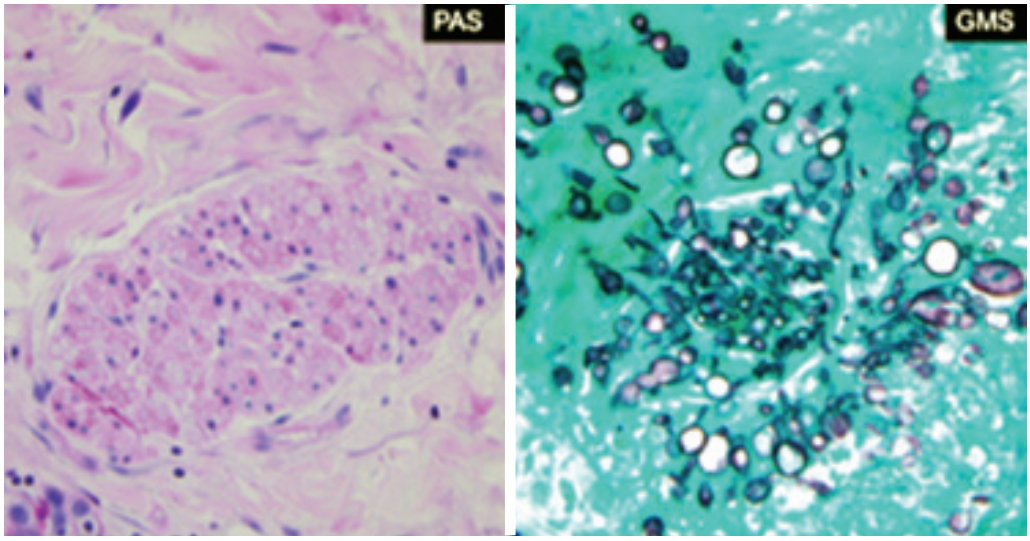

Figure 4. Biopsy from patient B. Septate hyphal elements seen on PAS and GMS stains

and mucous membranes (1-4). In humans, *Fusarium* causes a range of superficial, locally invasive, and systemic disease states that are closely related to the host's immune status. In those with intact immune systems, fusarial keratitis and onychomycosis are the most common infections (3). Risk factors for disseminated infections include neutropenia, lymphopenia, graft versus host disease, and prolonged corticosteroid therapy (5). Immunocompromised patients are at risk for systemic infection such as invasive sinusitis, pneumonia and fungemia (3).

Fusarium is notable for its relative resistance to most antifungal agents available. Currently, the most common treatments for fusariosis are limited to voriconazole, posaconazole, and amphotericin B. At the moment, there is no solid evidence to support the use of combination therapy. In patients with compromised immune system, it has been suggested that the decreasing immunosuppression should be considered in the setting of infection in order to maintain and stimulate body's own immune defenses (6). This can be achieved by decreasing or stopping the respective chemotherapy, using granulocyte stimulating factors, and/or granulocyte transfusions.

While the mortality rate in disseminated *Fusarium* infections is extremely high, the delay of diagnosis and initiation of treatment may also have an impact on survivorship. Unfortunately, presenting symptoms including the skin findings are often nonspecific; blood and tissue culture may also take hours to days. Furthermore, standard antimicrobial prophylaxis such as micafungin or itraconazole does not provide adequate coverage for *Fusarium*. The preferred antifungal prophylaxis against invasive molds such as *Fusarium* and *Aspergillus* is posaconazole; however, even that may not be sufficient for patients with persistent neutropenia (7). Until better prophylactic management in immunosuppressed patients can be achieved, a high index of suspicion along with prompt diagnosis and treatment are paramount for the treatment of disseminated *Fusarium* infection.

Abbreviation

ALL – acute lymphoblastic leukemia
PAS – periodic-acid Schiff
GMS – Gomori methenamine silver
SYK – spleen tyrosine kinase

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Diseminovane *Fusarium* infekcije kod akutne limfoblastne leukemije

Sažetak

Fusarium je sveprisutna vrsta gljivica koja se može naći u tlu i vodi. I dok *Fusarium* može izazvati lokalizovanu infekciju kod zdravih osoba, ipak najčešće napada osobe sa kompromitovanim imunosistemom, pogotovo one sa produženom neutropenijom. Stopa smrtnosti od sistemske infekcije je blizu sto posto. Ovde su prikazana dva slučaja diseminovane *Fusarium* infekcije kod dva pacijenta sa akutnom limfoblastnom leukemijom zajedno sa pregledom literature koja se odnosi na profilaksu i lečenje.

Ključne reči: Akutna limfoblastna leukemija; Fusarioza; Prikazi slučajeva; Imunokompromitovani bolesnici

Received 27 March, 2018
Accepted 8 April, 2018

DOI: 10.2478/sjdv-2018-0008

Cutaneous Polyarteritis Nodosa: Uncommon and Rare Form of Cutaneous Vasculitis

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UDC 616.5-001-02:616.13-002

Abstract

Cutaneous polyarteritis nodosa (CPAN) is a variant of polyarteritis nodosa that is limited primarily to the skin. It is a chronic recurrent disorder characterized by the presence of nodular lesions with or without ulceration on the distal third of the lower limbs. Nodular vasculitis and thrombophlebitis can be clinically or pathologically mistaken for CPAN. We present a case of a 51-year-old woman with painful nodules on the lower limbs. Some of the nodules were ulcerated. Histopathological examination of a nodule on deep incisional biopsy revealed fibrinoid necrosis of a medium-sized artery in the subcutis along with perivascular mixed infiltrate. The patient did not have any symptoms or signs of internal organ involvement. The possible etiological factor has not been detected. The patient was treated with oral prednisone 0.5 mg/kg/day and dapson 150 mg/day. Over the one-year follow-up the lesions showed regression, with one minimal relapse which resolved after the short course of oral prednisone.

Key words: Polyarteritis Nodosa; Skin Diseases; Chronic Pain; Prednisone; Biopsy; Treatment Outcome

Introduction

Cutaneous polyarteritis nodosa (CPAN) is a chronic, recurrent vasculitis that affects small arteries and arterioles in the panniculus and the dermal-subcutaneous junction (1). It still remains controversial whether CPAN is a skin symptom of polyarteritis nodosa (PAN), or a distinct clinical entity with different pathogenesis (2). The common clinical features of CPAN are multiple subcutaneous nodules or livedo and macules, with or without ulceration, affecting the lower extremities. Other symptoms may be associated with CPAN, such as constitutional, neurological, and musculoskeletal ones, limited to the affected areas (1, 3). Nodular vasculitis and thrombophlebitis can be clinically or pathologically mistaken for CPAN (4). The diagnosis is based on skin biopsy, as there are no specific serological tests (5).

Case Report

A 51-year-old woman presented with the erythematous, painful nodules on the lower limbs lasting for 7 months. The lesions were first diagnosed and treated as vasculitis nodularis with no improvement. On admission in our Clinic, physical examination showed asymmetrical, tender painful nodules and irregular ulcerated subcutaneous nodules over both legs (Figures 1 and 2). Routine investigations, including erythrocyte sedimentation rate, C-reactive protein, complete blood count with differential, blood levels of electrolytes and glucose, liver and renal function tests and urinalysis were normal. Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and anti-streptolysin-O were normal or negative. Serology tests for hepatitis B, C and HIV 1/2 were negative. QuantiFERON-TB Gold test was negative. Chest X-ray, echocardiography of the heart and ultrasonography of the abdomen showed no pathologic findings. The patient did not have any symptoms or signs of internal organ involvement. Deep incisional skin biopsy of the nodulus revealed fibrinoid necrosis of small arteries in the subcutis along with perivascular mixed infiltrate (Figures 3 and 4). The patient was treated with oral prednisone 0.5 mg/kg/day and dapson 150 mg/

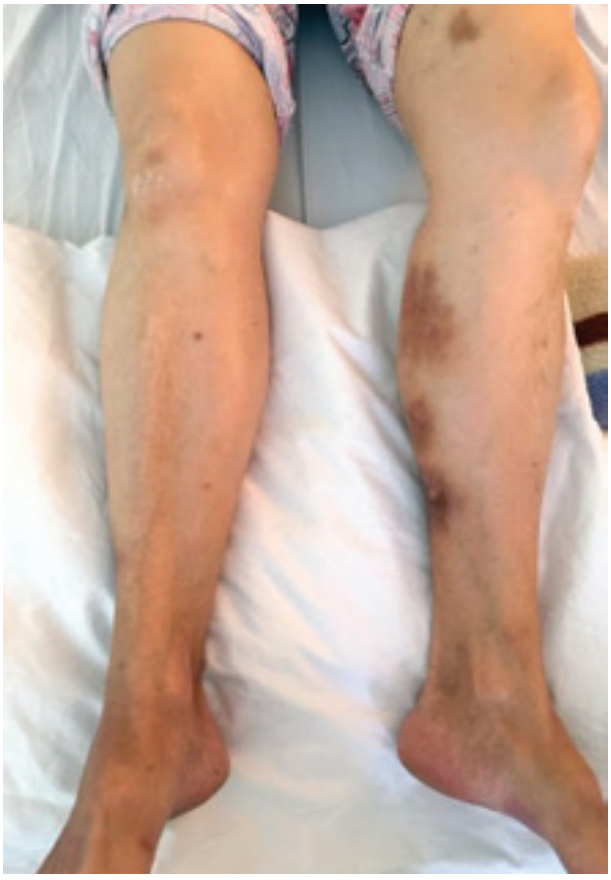

Figure 1. Reddish-purple nodules on the lower extremities

day. After 2 months, the lesions showed regression with residual hyperpigmentation and scarring and the dose of prednisone was then slowly decreased and discontinued. In further 10 months the patient experienced one minor relapse, therefore she received another course of prednisone for several weeks. On the last check-up, 12 months after the hospitalization, the patient was free of active lesions.

Discussion

CPAN was initially described in 1931 by Lindberg as the case of necrotizing vasculitis, which was limited to the skin but could not have been histopathologically distinguished from systemic PAN (6). CPAN more frequently affects women (male: female ratio = 1:1.7), aged ≥ 40 years, with numbers of patients peaking at 50–59 years of age (7). The lesions commonly occur on the legs in 97%, followed by the arms in 33%, and the trunk in 8% of patients. Additional involvement of the head and neck has been noted in 9 of 23 patients (39%) with CPAN (3). The skin manifestations of CPAN include subcutaneous nodules (80-100%), livedo reticularis (45-80%), ulcers, and gangrene. Other findings include purpura, papules, atrophie blanche, and leg edema. The nodules frequently have a diameter of 5-15 mm and are multiple, red-dark to reddish-purple, and are accompanied by spontaneous pain and tenderness. These nodules, with or without livedo reticularis, are usually the first presentation of the disease, and are the predecessor to ulceration in 50-59% of

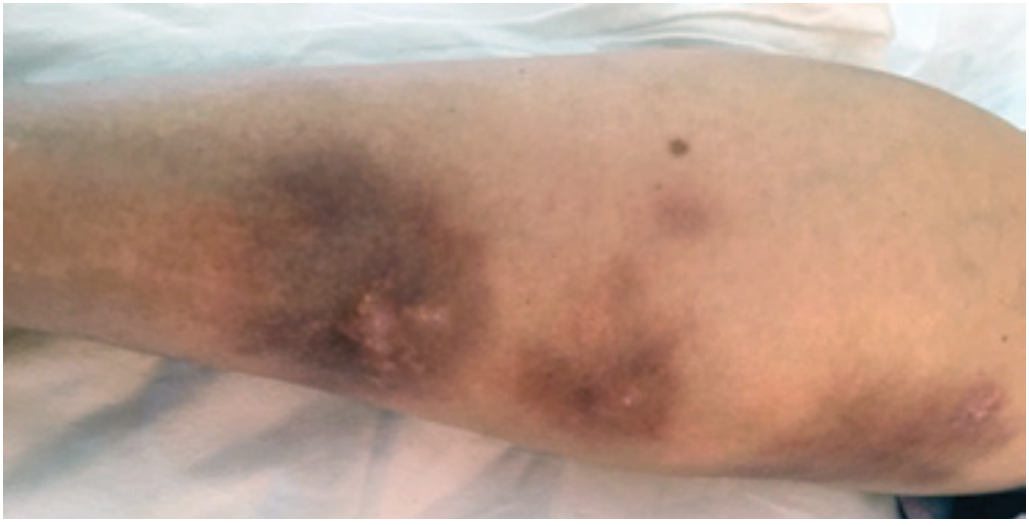

Figure 2. Erythematous nodule with a central crust on the left leg

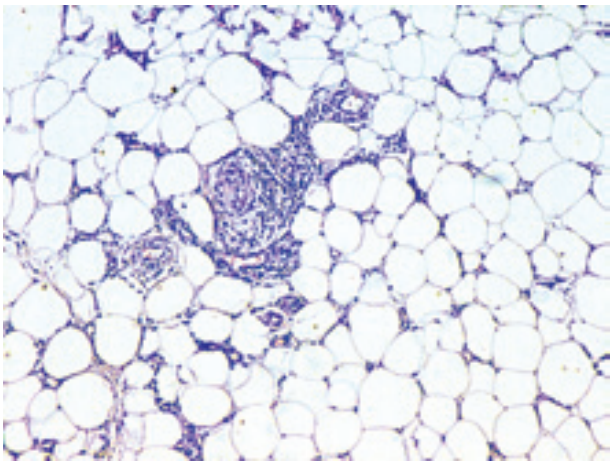

Figure 3. Fibrinoid degeneration of the vessel wall with perivascular mixed infiltrate of lymphocytes, histiocytes and a few neutrophils into the subcutis (haematoxylin-eosin stain ×100)

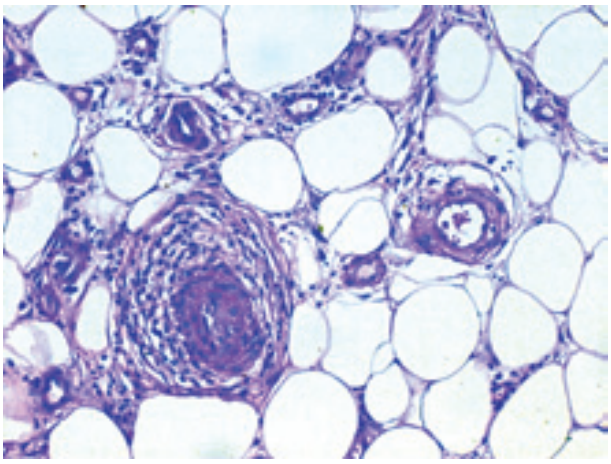

Figure 4. Fibrinoid degeneration, intimal proliferation and an almost complete obliteration of the vessel wall lumen (Periodic acid-Schiff stain ×200)

the cases (2, 7, 8). Extra-cutaneous manifestations of CPAN include constitutional symptoms, fever, myalgias, arthralgias, and peripheral neuropathy (mononeuropathy and mononeuritis multiplex) (3). In the patients with an ulcerated CPAN, a more chronic course of the disorder with neurological involvement is common (8). Unlike the systemic disease, CPAN does not show immunologic abnormalities (9). Absence of the life-threatening organ involvement in CPAN (renal ischemia, testicular pain/epididymitis, ischemic myalgia and hypertension) distinguishes CPAN from the systemic PAN (10). Our patient did not have any symptoms or signs of the internal organ involvement.

The diagnosis of CPAN is based on clinical features of isolated skin involvement confirmed by histopathological findings (5). Deep, surgical incisional biopsies are essential for the correct diagnosis of CPAN. A punch biopsy is not recommended, because it often fails to sample larger vessels that are typically affected (4). Serial sections may also be necessary to demonstrate the vasculitis, particularly when the involvement is segmental and focal (9). The microscopic findings of CPAN can be divided into four stages: (1) degenerative stage with degeneration of arterial wall and deposition of fibrinoid material and partial or complete destruction of internal and external elastic laminae; (2) acute inflammatory stage with an infiltrate mostly composed of neutrophils with some eosinophils around and within the arterial wall; (3) granulation tissue stage with an infiltrate also containing lymphocytes and macrophages and intimal proliferation and thrombosis with occlusion of the lumen leading to ulceration; and (4) healed end-stage with fibroblastic proliferation extending in the perivascular area (4, 11).

Nodular vasculitis is a lobular panniculitis and vasculitis affecting mostly venules or septal veins and less commonly arteries. In contrast, CPAN is an arterial vasculitis with minimal extension of its inflammation into the adjacent subcutis. The pattern of elastic tissue distribution and vessel silhouette is a diagnostic aid to differentiate between venous and arterial vasculitis (4). Superficial thrombophlebitis is a sequela of degenerative or anatomical alterations of vessel walls in lower legs, slowed blood flow, and/or hypercoagulable conditions, which then secondarily lead to inflammatory infiltration (1). Two other entities have recently been described, macular arteritis and lymphocytic thrombophilic arteritis that show clinical features of CPAN but a lymphocytic arteritis on biopsy (12, 13). These variants of vasculitis may simply represent latent or late evolutionary stages of CPAN (4). The etiology of CPAN is unknown. Associations with various viral (particularly HBV as well as HCV, HIV 1/2 and parvovirus B19) and group A streptococcal infections have been reported (2). Minocycline-induced CPAN is a well documented

phenomenon (14). In our patient, a possible etiological factor has not been detected.

Systemic corticosteroids remain the mainstay of treatment for CPAN and most patients seem to respond to oral prednisone. Successful treatment outcomes were reported with dapsone, colchicines, azathioprine, methotrexate, cyclosporine, cyclophosphamide, NSAIDs, sulphapyridine, pentoxyphylline, and intravenous immunoglobulin. Antibiotic treatment may be needed in patients with documented streptococcal or other bacterial infections (2, 3). The prognosis of CPAN is favorable with no known mortality from the disease itself. The course is chronic with relapses and remissions that may occur spontaneously or following treatment (5). However, since progression to systemic PAN may occur in some patients, careful follow-up is necessary (7).

In summary, CPAN is a rare and benign cutaneous vasculitis of unknown etiology and can be challenging to diagnose and manage. There are no specific clinical and laboratory findings. The diagnosis is based on clinical features of isolated skin involvement confirmed by histopathological findings. Systemic corticosteroids and dapson are effective in the treatment of CPAN. Long-term follow-up is necessary for CPAN because it can progress to systemic PAN.

Abbreviations

CPAN – cutaneous polyarteritis nodosa
PAN – polyarteritis nodosa

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Kutani poliarteritis nodoza: neobičan i redak oblik kutanog vaskulitisa

Sažetak

Kutani poliarteritis nodoza predstavlja varijantu nodoznog poliarteritisa koja je ograničena samo na kožu. Kutani poliarteritis nodoza ima hronični, rekurentni tok i klinički se manifestuje u vidu nodusa sa ulceracijom ili bez nje, lokalizovanih na distalnim trećinama donjih ekstremiteta. U praksi se često klinički i histopatološki dijagnostikuje kao vaskulitis nodularis ili tromboflebitis. Prikazujemo pacijentkinju uzrasta 51 godinu sa bolnim nodusima na donjim ekstremitetima, od kojih su pojedini bili egzulcerisani. Histopatološki nalaz duboke incizione biopsije nodusa pokazao je fibrinoidnu nekrozu arterija srednjeg kalibra u supkutisu i mešoviti

perivaskulni infiltrat. Pacijentkinja nije imala nijedan simptom ni znak sistemskog vaskulitisa. Mogući etiološki faktor nije detektovan. Pacijentkinja je lečena prednizonom 0,5 mg/kg/dan i dapsonom 150 mg/dan. Došlo je do regresije promena tokom narednih godinu dana, uz jedan minimalan recidiv nakon nekoliko meseci koji je rešen kratkotrajnom primenom prednizona.

Ključne reči: Poliarteritis nodoza; Kožne bolesti; Hronični bol; Prednizon; Biopsija; Ishod terapije

Received 4 September, 2018
Accepted 15 September, 2018

DOI: 10.2478/sjdv-2018-0009

Allergic Contact Dermatitis Caused by Homemade Slime

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UDC 616.5-002.1-053.2:613.63

Abstract

Nowadays, allergic reactions in children are seen in dermatological practice on a daily basis. The most common reasons for allergic contact dermatitis (ACD) are piercings, temporary tattoos, a wide range of cosmetic products, substances related to the practice of a variety of hobbies and sports, etc. Slime is a new hobby and has become an obsession for some kids. There are many homemade slime recipes. The most common recipe for slime is glue, borax and food coloring for all kinds of rainbow effects. We present a case of an 11–year–old Caucasian girl with hand contact dermatitis caused by an allergic reaction to Slime.

Key words: Dermatitis, Contact; Play and Playthings; Safety; Child; Borates; Adhesives; Food Coloring Agents
Non MeSH: Slime

The frequency of allergic contact dermatitis (ACD) worldwide is reported to be between 15 and 71%. In Bulgaria it is around 42% (according to the author's data gathered between 2013 and 2017 in 78 children in whom patch test had been performed). Kazandjieva J. Masterclass Pediatric dermatology Sofia 3-6.06.16.

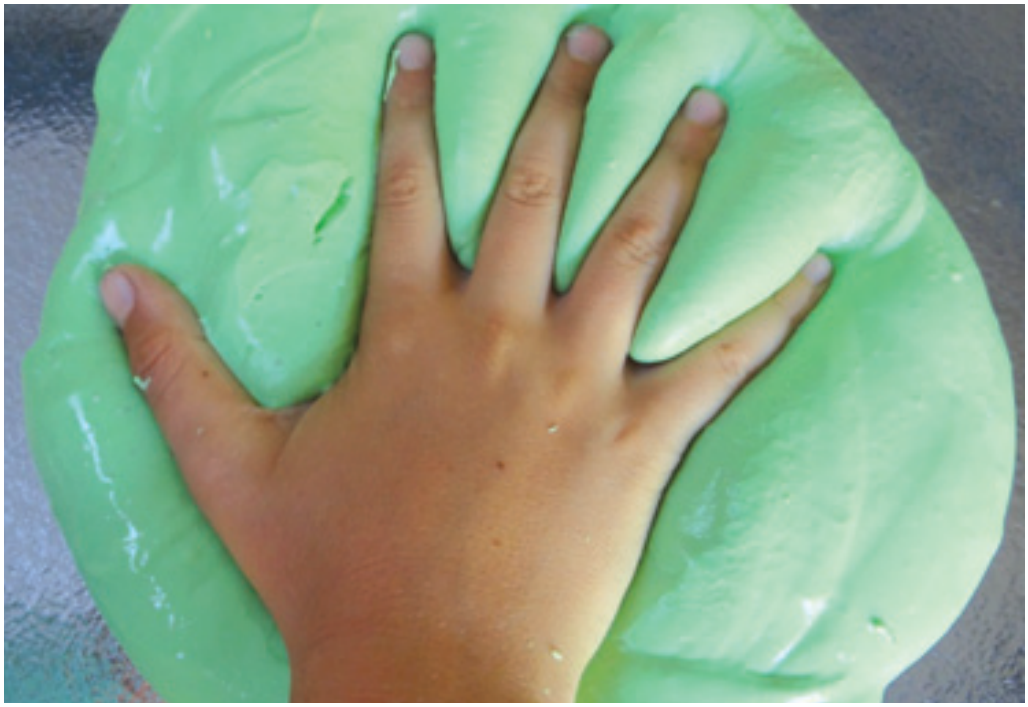

Figure 1. Homemade Slime

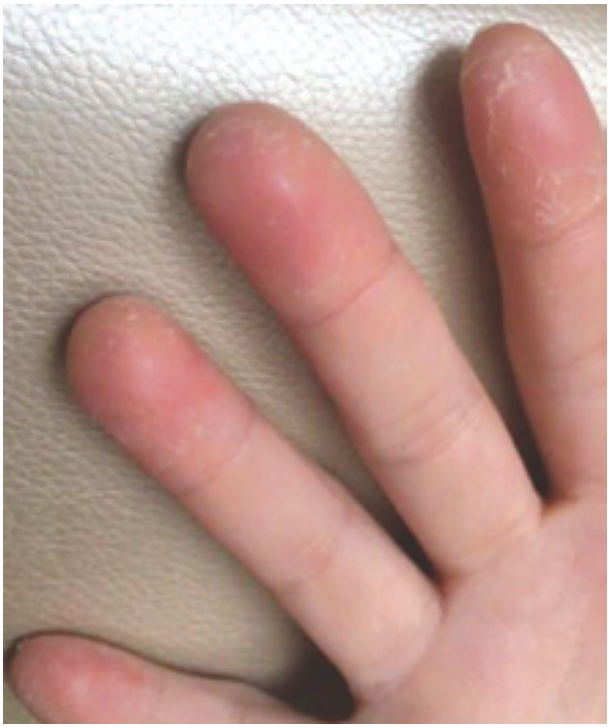

Figure 2. Contact dermatitis on the fingers

Nickel, cobalt, Balsam of Peru and parafenilendiamina were the most frequent sensitizers.

In recent years, there has been a significant increase in the frequency of ACD in children that is possibly related to the prolonged contact with allergic substances inherent to different hobbies in everyday life.

Case Report

An 11-year-old female patient presented with suddenly appearing itchy rash on the palms and fingers. The patient and her mother associated the appearance of the rash with her new hobby, making a slime (Figure 1).

The treatment with a wide range of topical corticosteroids yielded good results.

On clinical examination, the skin changes were localized on both hands. Erythema and desquamation were present (Figures 2 and 3).

Routine laboratory findings were within the normal ranges. The microbiological and mycological examinations were negative.

Patch testing with European baseline series (Chemotechnique Diagnostics) was performed. Positive reactions to Kathon(+++),

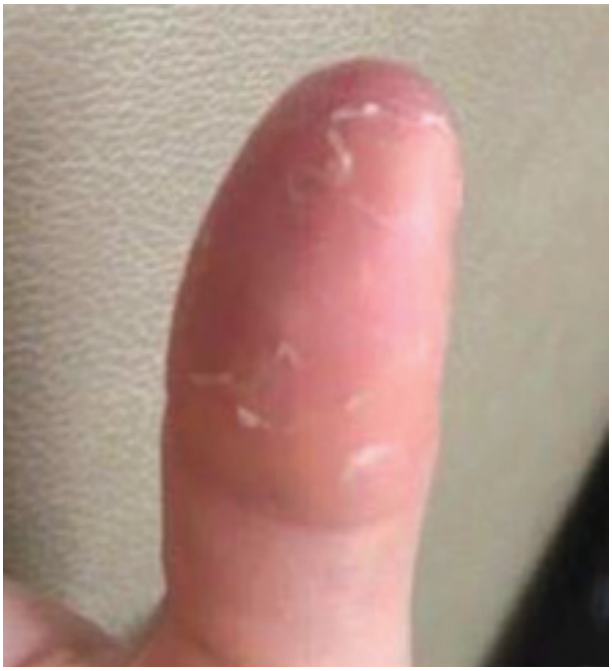

Figure 3. Erythema and desquamation on the finger

and Methylisothiazolinone(++), were detected (Figure 4).

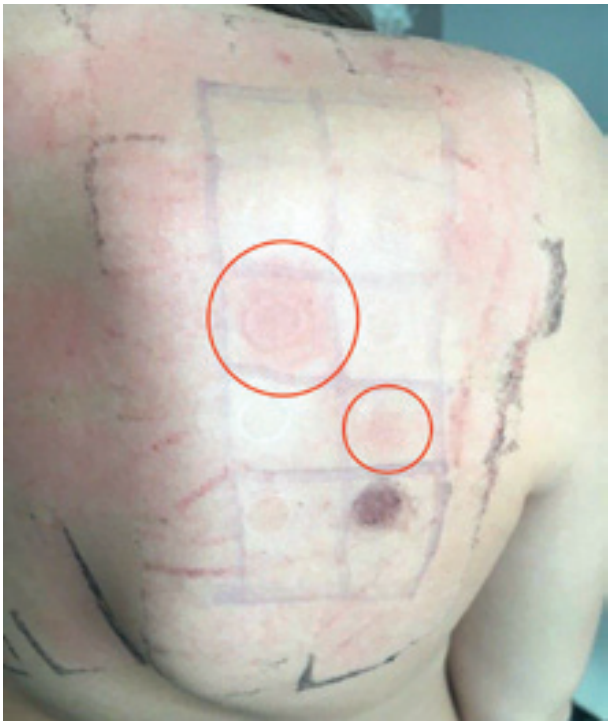

Figure 4. Positive reactions to Kathon (+++), and Methylisothiazolinone (++)

Discussion

Slime is a new hobby and has become an obsession for some kids. There are many different types of slime (Soft Serve, Fluffy Slime, Clear Slime, Foam, etc.)

The most common recipe for homemade slime is glue, borax and food coloring.

Our patient made her slime with borax and glue without color.

We reviewed the literature looking for the main ingredients glue and Borax, and we found that the glue, which had been used by our patient, contained Methylisothiazolinone.

Boric acid and Sodium borate (Borax) are used in household cleaning, in many detergents, cosmetics, and enamel glaze (1, 2).

Literature offers a lot of reports on boric acid toxicity and fatalities (3). The main symptoms from Borax poisoning are vomiting, diarrhea, seizures, skin erythema looking like "boiled lobster", and extensive desquamation after a few days (4, 5). There are many reported cases about toxicity, but there is no evidence about skin allergy reactions to Borax.

Methylisothiazolinone (MI) has been commonly used as an antimicrobial and antifungal preservative in different cosmetics, household products, such as moist wipes, shampoos, cleaners (6, 7). As a mixture, Kathon™ CG (methylchloroisothiazolinone/MI) is also used in paints, glues, washing tanks and adhesives (8,9).

Nowadays, MI is one of the most common causes of allergic contact dermatitis, because it is actually present in the most used preservatives.(10). The frequency of contact allergy to MCI/MI and MI is decreasing (11,12).

The Slime is usually used by young children, and it may be good to know that its main ingredients, glue and Borax, are toxic and can cause allergic reactions on the skin.

Conclusion

According to our knowledge this is the first reported case of contact dermatitis caused by Slime.

MI is one of the most common causes of allergic contact dermatitis. In recent years, there has been a significant increase in the frequency of ACD in children, and some of the reasons are new hobbies, involving homemade products.

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Alergijski kontaktni dermatitis izazvan „ljigavcem" napravljenim u kućnim uslovima

Sažetak

Danas se alergijske reakcije kod dece viđaju u svakodnevnoj dermatološkoj praksi. Najčešći uzroci alergijskog kontaktnog dermatitisa su pirsing, privremene tetovaže, širok spektar kozmetičkih proizvoda, supstance povezane sa raznim hobijima i sportovima itd. Ljigavac je novi hobi i postao je prava opsesija kod neke dece. Ima mnogo recepata da se napravi ljigavac kod kuće. Najčešći recept za ljigavca je lepak, boraks i prehrambena boja za sve vrste efekta duge. Prikazujemo slučaj devojčice, belkinje, stare 11 godina sa kontaktnim dermatitisom na ruci izazvanim alergijskom reakcijom na ljigavca.

Ključne reči: Kontaktni dermatitis; Igra i igračke; Bezbednost; Dete; Borati; Adhezivi; Boje za hranu
Ne MeSH: Ljigavac

Received 6 September, 2018
Accepted 29 October, 2018

DOI: 10.2478/sjdv-2018-0010

DERMOSCOPY OF THE MONTH
Dermoscopy of Primary Cutaneous B-Cell Lymphoma

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UDC 616.5-006.44-072

Abstract

Primary cutaneous B- cell lymphomas (PCBLs) are B-cell malignant neoplasms that originate in the skin, and have no extracutaneous manifestations of disease at the time of diagnosis. PCBLs are classified into three main types: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL- LT). Dermoscopic characterization of PCBLs has been limited and dermoscopy may help to augment the clinical recognition of PCBLs with the most common dermoscopic findings of salmon colored areas and serpentine vessels. Recognition of dermoscopic features of primary cutaneous B- cell lymphomas can improve the early diagnosis of these tumors and their proper management.

Key words: Lymphoma, B-Cell; Dermoscopy; Skin Neoplasms; Early Diagnosis; Case Reports

Introduction

Primary cutaneous B-cell lymphomas (PCBLs) are B-cell malignant neoplasms that originate in the skin, and have no extracutaneous manifestations of disease at the time of diagnosis. PCBLs are classified into three main types: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL- LT). The first two types are recognized as indolent forms, and the third one has aggressive behavior (1). While dermoscopic features of melanoma and non-melanoma skin cancers are largely defined, dermoscopic characterization of PCBLs has been limited. Recently, case reports (2, 3) and small case series (4) have suggested that dermoscopy may help to improve the clinical recognition of PCBLs with the most common dermoscopic findings of salmon colored areas and serpentine vessels. The presence of these features, however, is not sufficient to differentiate PCLBs from wide spectrum of

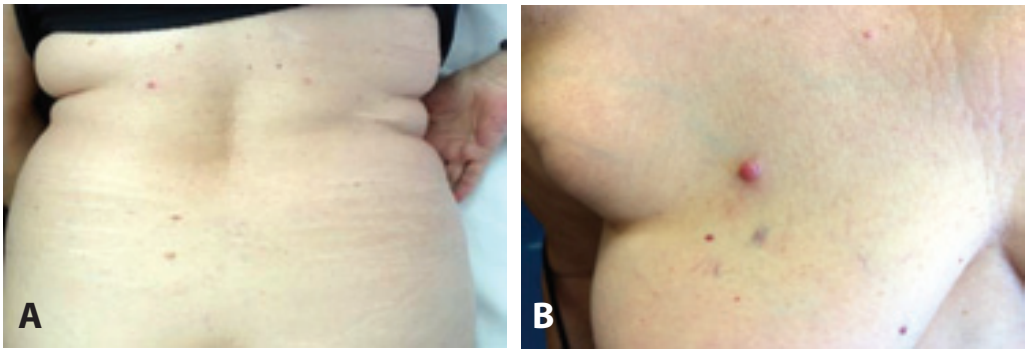

Figure 1. A, B Multiple nodular lesions on the trunk

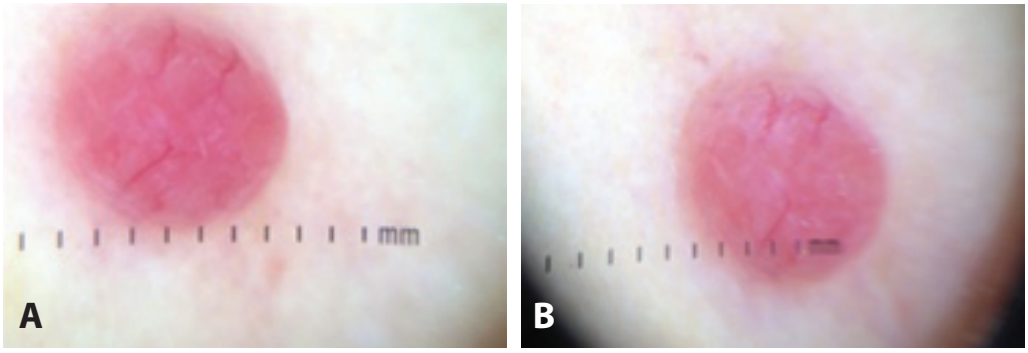

Figure 2. A, B Multiple nodular non-pigmented lesions with fine, arborizing and linear irregular vessels on dermoscopy

other entities, such as BCC, insect bites and amelanotic melanoma.

Case Report

We present a 61-year-old female, who was followed up at our Department due to recent melanoma excision. During regular complete skin examination, new multiple nodular non-pigmented lesions on the trunk were noticed that had appeared in the previous 3 months (Figure 1).

Dermoscopy of the lesions showed fine, arborizing and linear irregular vessels on the pinkish background (Figure 2).

Multiple nodular basal cell carcinomas were the initial clinical diagnosis, and surgical excision was performed. Histopathological analysis revealed low grade mature B-cell cutaneous non-Hodgkin's lymphoma with plasmocyte differentiation (primary cutaneous marginal zone lymphoma).

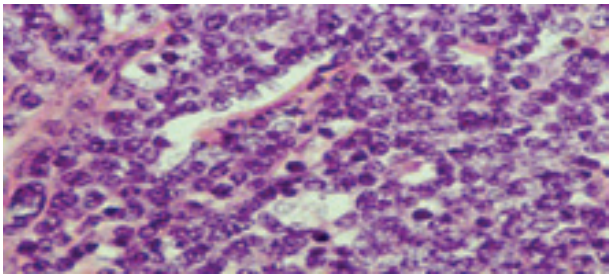

Figure 3. Low grade mature B-cell cutaneous non-Hodgkin's lymphoma, with plasmocyte differentiation

Lymphoid cells in the infiltrate expressed CD138, CD20 and MUM1, while CyclinD1, CD23, CD5, TdT and CD3 were considered

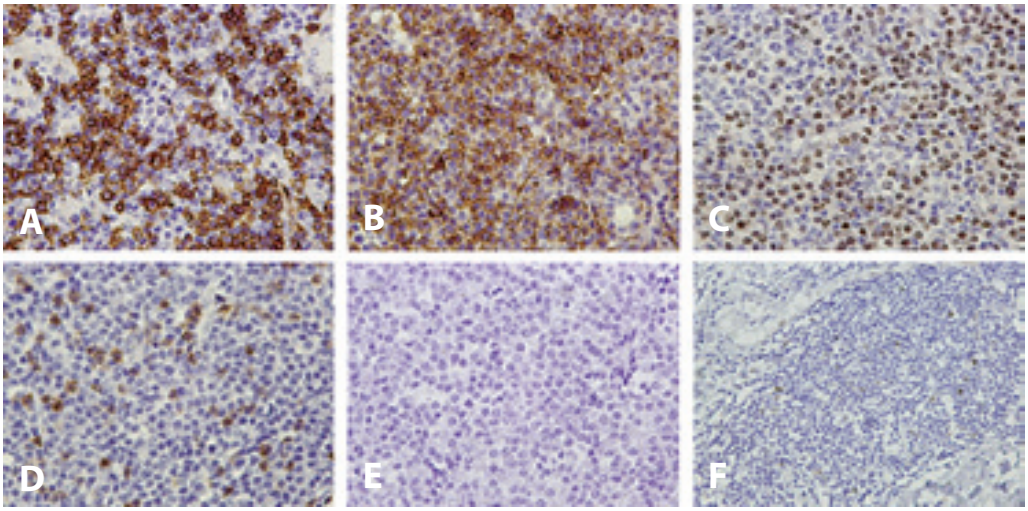

Figure 4. Immunohistochemistry A . CD138+ (x400) B. CD20+ (x400) C. MUM1+ (x400) D. CyclinD- (x200) E. CD23- (x400) F. CD3- (x400)

negative on immunohistochemistry profiling (Figure 4).

Laboratory analyses, ultrasonography of peripheral lymph nodes and CT findings where within normal range. There was no pathologic infiltration on bone marrow biopsy. The presence of a polyclonal B-cell population was detected in the blood, while it was monoclonal in the skin sample (5).

The therapeutic option was surgical excision, which is the first-line recommended treatment of PCBCL based on current guidelines (6).

Discussion

The clinical presentation of cutaneous lymphomas can be non-specific, and biopsy with histopathological analysis is necessary for a definitive diagnosis. Few studies and case series evaluated the diagnostic value of dermoscopy in cutaneous lymphoma (3, 4). The dermoscopic features that were reported for PCBCL lesions included white circles, salmon colored areas, scales, arborizing vessels or a polymorphous vascular pattern. In a retrospective study of 58 PCBCL, the most frequent dermoscopic features were salmon-colored background area and prominent serpentine blood vessels, and the lesions were most commonly localized on the trunk (7).

The increased vascularity in PCBCL is attributed to the angiogenesis that accompanies the neoplastic process. Although salmon-colored background and serpentine like vessels can suggest the diagnosis of cutaneous lymphoma, they are not specific and can raise wide clinical differential diagnosis spectrum of malignant and inflammatory conditions, as was shown in the retrospective study of 172 patients with biopsy proven PCBCL. In this study, the most common differential diagnoses were basal cell carcinoma, squamous cell carcinoma and dermatofibrosarcoma protuberans, while cutaneous metastasis and melanoma were suspected less frequently. Other non-neoplastic conditions, such as cyst, granulomatous processes and infectious disease were also taken into consideration (7).

Conclusion

Recognition of dermoscopic features of primary cutaneous B-cell lymphomas can improve the early diagnosis of these tumors and their proper management. For the diagnosis of PCBCL, clinical picture, dermoscopy, histopathology, immunohistochemistry and molecular studies are necessary. Although salmon colored and serpentine like vessels are frequently seen dermoscopic features of PCBCL, they are not specific and should be correlated to clinical findings.

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Dermoskopija primarnih kutanih B-ćelijskih limfoma

Sažetak

Primarni kutani B-ćelijski limfomi su maligne neoplazije koje vode poreklo od B-ćelija kože, u trenutku postavljanja dijagnoze najčešće nemaju ekstrakutane manifestacije. Klasifikovani su u tri osnovne grupe: primarni kutani B-ćelijski limfomi marginalne zone, primarni kutani B-ćelijski limfomi folikularnog centra i difuzni limfomi velikih B-ćelija. Dermoskopija može doprineti ranijem postavljanju dijagnoze kutanih B-ćelijskih limfoma, a najčešće dermoskopske karakteristike su polja boje lososa i zmijoliki krvni sudovi. Prepoznavanjem dermoskopskih karakteristika ove vrste limfoma i ranijim postavljanjem dijagnoze, možemo doprineti i ranijem započinjanju lečenja, kao i njegovom boljem ishodu.

Ključne reči: B-ćelijski limfom; Dermoskopija; Kožne neoplazme; Rana dijagnoza; Prikazi slučajeva

Received 10 August, 2018
Accepted 20 August, 2018

Report on the 8th Post-Chicago Meeting on Melanoma/Skin Cancer

The 8th Post-Chicago Meeting on Melanoma/Skin Cancer was held on the 28th and 29th of June, 2018 in Leonardo Royal Hotel in Munich. Prof. Axel Hauschild and Prof. Claus Garbe presided the Congress. The Post-Chicago Meeting 2018 was attended by more than 700 participants working in the field of dermatology, medical oncology, immunology, radio oncology and other specialties from more than 35 countries. The interactive Congress offered a comprehensive overview on all new developments in melanoma diagnostics and therapy and a direct communication with the world leading experts in these fields. A wide spectrum of topics in dermato-oncology was covered during the 2-day program. International key opinion leaders on melanoma were invited to give an overview through specified presentations, to present the latest clinical trial results, and to discuss on exciting new drugs with the audience.

Our delegation consisted of two participants. Prof. Lidija Kandolf Sekulović was a chairperson together with Prof. Alexander Stratigos in the session "Recent advances in the treatment of non-melanoma skin cancer". Prof. Željko Mijušković presented two interesting melanoma cases in the EADO Forum session.

Due to the continuous increase in the number of participants, the next Post-Chicago Meeting will take place in the Hotel Hilton Tucherpark in Munich from the 21st to the 22nd of June, 2019.

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Figure 1. From left to right: Prof. Claus Garbe (President of EADO), Prof. Lidija Kandolf Sekulović and Prof. Željko Mijušković

Report on the 15Th Spring Symposium of the European Academy Of Dermatology and Venereology, Budva 2018

The 2018 Spring Symposium was held in beautiful Montenegro, whose name was derived from Venetian Italian in reference to Mount Lovćen, once covered by an impenetrable "black" forest.

The picturesque city of Budva/Bečići, with its hotels "Splendid" and "Mediteran" at the Adriatic Sea, was the venue of the Symposium, from the 3rd to 6th of May, 2018. The coastal area around Budva is the center of Montenegrin tourism, known for its well-preserved medieval walled city, sandy beaches and diverse social life. Budva is 2,500 years old, which makes it one of the oldest settlements on the Adriatic coast.

The 2018 Spring Symposium programme covered a wide range of practical relevant subjects, including eczemas through the ages, skin cancers, dermoscopy, infectious diseases and sexually-transmitted diseases. The plenary lectures and "what's new" session gave further highlights on melanoma, acne and rosacea, bullous diseases, and pediatric dermatology as well as many other issues. The Scientific Programming Committee succeeded at assembling the prominent speakers who spoke on interesting contemporary topics, thus satisfying the needs and expectations of both the young and the experienced dermatovenereologists. The intensive 3-day program included 35 stimulating sessions (Review and Updates, Plenary Lectures, Free Communications, What's New) with 109 lectures and oral presentations. There were 544 e-Poster presentations.

Figure 1. Prof. Miloš Nikolić presenting the lecture "Treatment of severe alopecia areata".

The President of the European Academy of Dermatology and Venereology (EADV), **Prof. Luca Borradori,** expressed his personal and

Figure 2. Associate Prof. Jelena Stojković Filipović presenting the lecture at the Session "Eczemas: Treatment".

Figure 3. Associate Prof. Dušan Škiljević, Associate Prof. Mirjana Gajić Veljić, Prof. Ljiljana Medenica and Prof. Andreas Katsambas (from Athens, Greece) at the dinner hosted by the President

sincere thanks to Dr. Predrag Štilet, the Chairman of the 15th Spring Symposium and the President of the Montenegrin Association of Dermatoveneorology, whose enthusiasm and drive made this event an unforgettable experience for all participants. He organized a memorable Networking Symposium, which gave the audience a true taste of Montenegro's cultural heritage. Dr. Štilet also presented the lecture "Medical and surgical treatment of condylomata" at the Review and Updates Session "Sexually Transmitted Infections".

The large participation of Serbian dermatovenereologists was highly evaluated. The number of the invited speakers from Serbia

Figure 4. Prof. Danijela Dobrosavljević Vukojević, Associate Prof. Jelena Stojković Filipović, Associate Prof. Mirjana Gajić Veljić, Associate Prof. Dušan Škiljević, Dr Margita Mijušković and Prof. Mirjana Milinković Srećković at the dinner hosted by the President

at the 15th EADV Spring Symposium in Budva was greater than ever before.

Assoc. Prof. Dušan Škiljević from Belgrade was the chairman at the Review and Updates Session "Cutaneous manifestations of infectious diseases" and he presented the lecture "Spectrum of staphylococcal skin infections".

Prof. Mirjana Milinković Srećković from Belgrade presented the lecture "Occupational dermatitis: Clinical spectrum" at the Review and Updates Session "Hand eczema".

Assoc. Prof. Jelena Stojković Filipović from Belgrade was the chairperson at the Review and Updates Session "Eczemas: Treatment" where she delivered the lecture "Corticosteroids and calcineurin antagonists".

Prof. Danijela Dobrosavljević from Belgrade was the chairperson at the Review and Updates Session "Dermoscopy" and she presented the lecture "Dermoscopic features of basal cell carcinoma".

Assoc. Prof. Danica Tiodorović from Niš delivered the lecture "Dermoscopy of nail and mucosal lesions" at "Dermoscopy" session as well.

Prof. Miloš Nikolić from Belgrade was the chairman at the Review and Updates Session "Hair disorders" where he delivered the lecture "Treatment of severe alopecia areata".

Prof. Ljiljana Medenica from Belgrade was the chairperson at the Plenary Lectures.

Prof. Ivana Binić from Niš was the chairperson at the Free Communications Session in miscellaneous.

There were 13 e-Poster presentations from Serbia.

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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:

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The title page should include the following information:

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– 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/.

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– 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.

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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.

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Народна библиотека Србије, Београд

616.5(497.11)

SERBIAN Journal of Dermatology and Venerology / editor-in-chief Lidija Kandolf Sekulović. - Vol. 10, no. 2 (June 2018). - Belgrade (Pasterova 2) : The Serbian Association of Dermatovenereologists, 2018- (Beograd : Zlatni presek). - 30 cm

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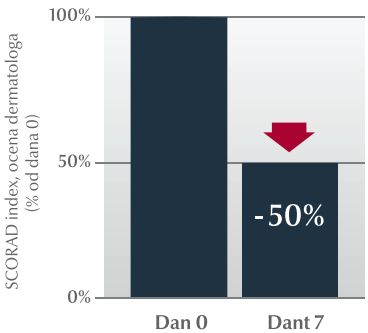

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