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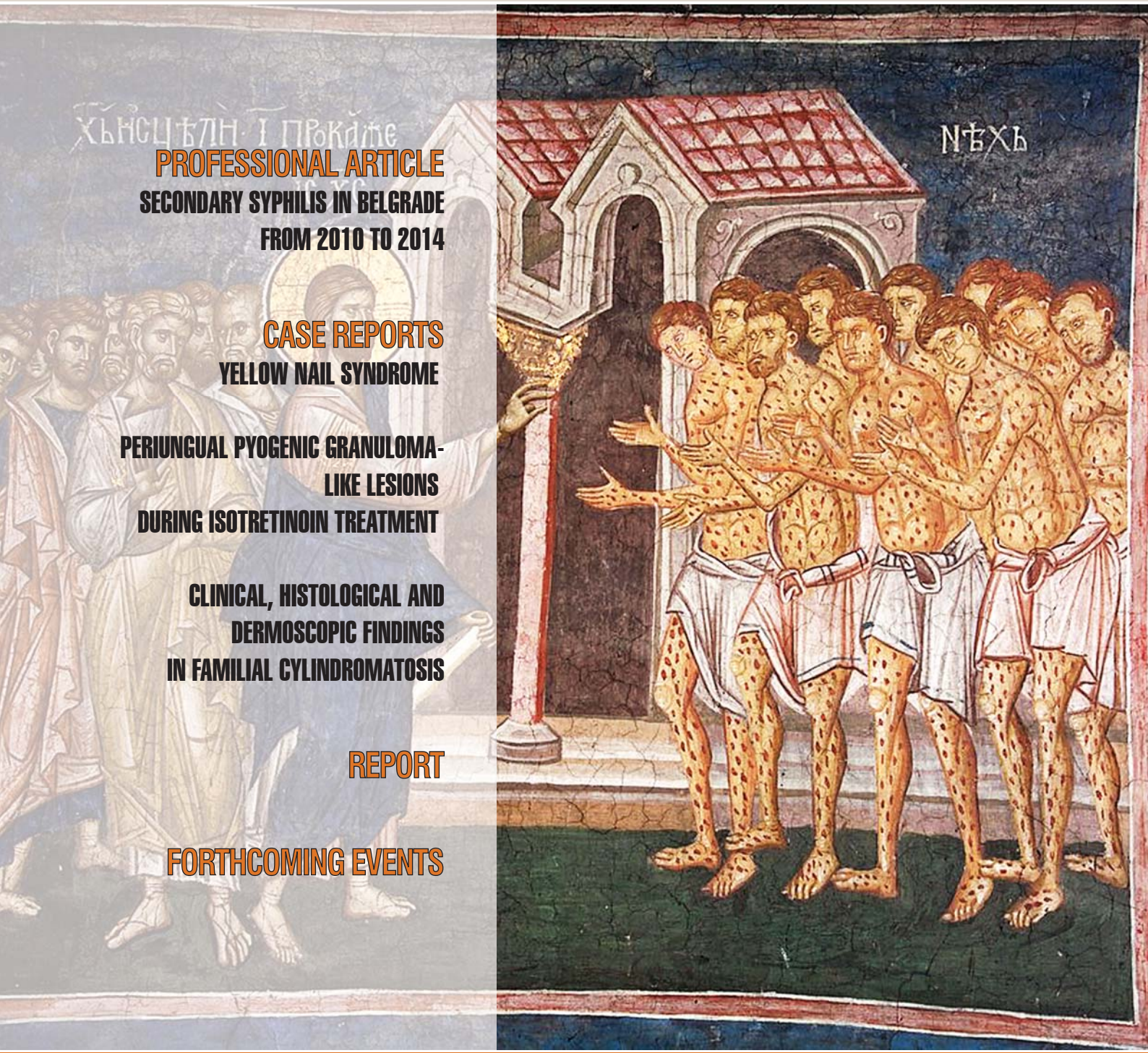

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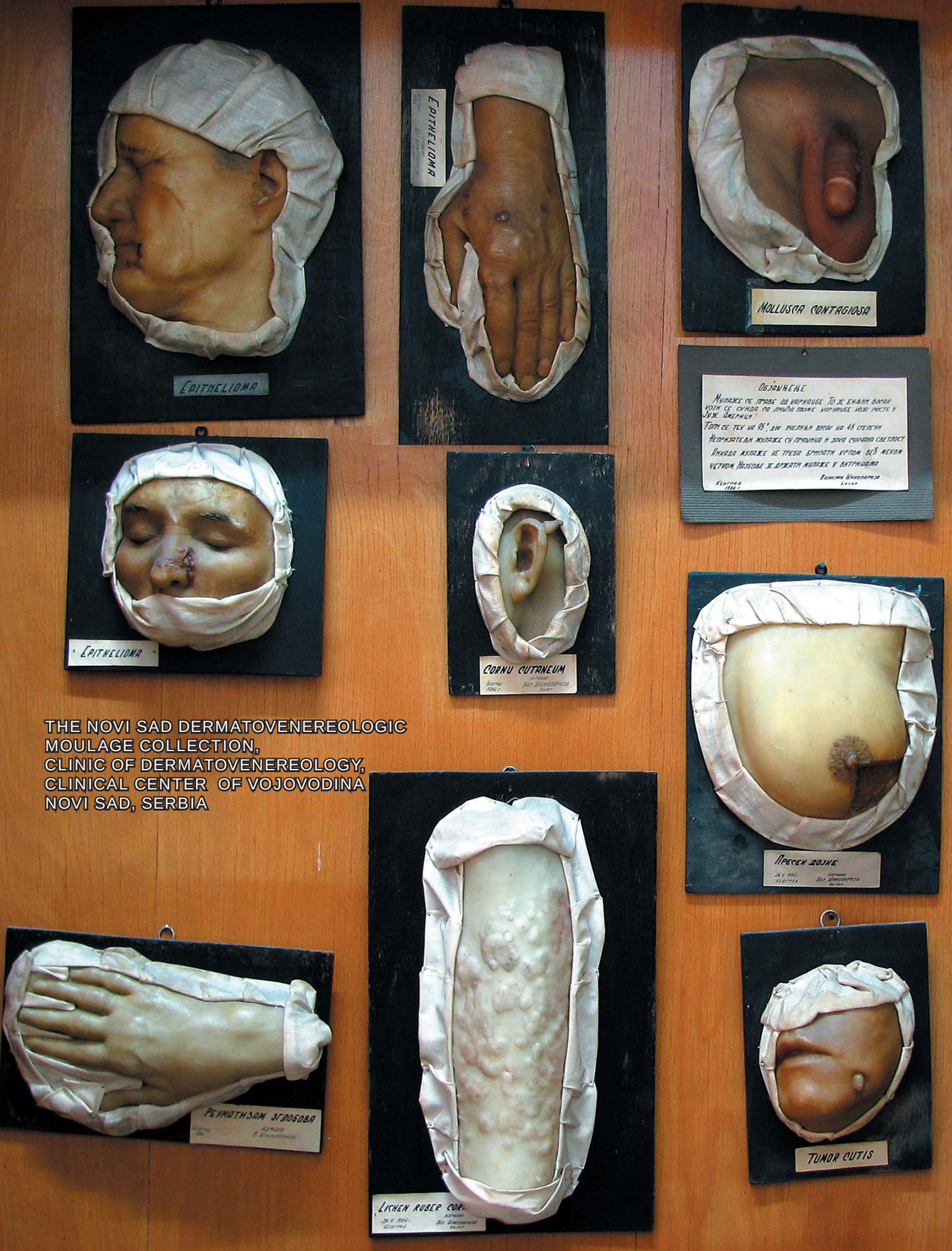

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Secondary Syphilis in Patients Treated at the City Institute for Skin and Venereal Diseases in Belgrade from 2010 to 2014

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Abstract

The aim of this study was to analyze the characteristics and clinical manifestations of secondary syphilis among patients registered at the City Institute for Skin and Venereal Diseases in Belgrade, during the period from 2010 to 2014. The study was designed as a case-note review. In the five-year period, a total of 62 patients with secondary syphilis were registered. The average patient age was 32 years. There were 45 (72.6%) HIV-negative, and 17 (27.4%) HIV-positive patients. The incidence of HIV–positive patients was significantly different from random distribution ($p = 0.016$). All HIV-positive patients were unmarried men. A significant percentage of HIV-positive patients were unemployed ($p < 0.001$), reported unknown source of infection ($p = 0.002$) and were all homosexuall ($p = 0.026$). More than 25% of all patients with syphilis had a history of chancres, and it was still present at the time of examination in 11.3% of all patients. The majority of cases (87.1%) had a rash, and lymphadenopathy was found in 20% of patients. However, syphilitic alopecia was detected only in HIV-positive cases ($p = 0.004$). There were no statistically significant differences between HIV-positive and HIV-negative patients in regard to other clinical manifestations, such as mucous patches and condylomata lata. Being a great imitator, secondary syphilis may manifest in a myriad of diverse morphological entities and clinical manifestations. We review a range of cutaneous manifestations of secondary syphilis and skin diseases it may mimic. Clinicians must be vigilant and consider syphilis in differential diagnosis, and maintain a high index of suspicion, especially when assessing vulnerable populations, such as men who have sex with men and HIV-infected individuals.

Key words

Syphilis; Syphilis, Cutaneous; Diagnosis; Sexually Transmitted Diseases; Homosexuality, Male; HIV Infections; Signs and Symptoms

Syphilis is an infectious disease caused by *Treponema pallidum*. If untreated, the disease passes through 4 stages: primary, secondary, latent and tertiary. Syphilis is transmitted almost exclusively by sexual contact, including oro-genital contact, via blood and blood products, or vertically from an infected mother, during pregnancy, birth or breastfeeding. In sexually acquired syphilis the incubation period is 10 - 90 days, when a painless chancre appears at the site of inoculation associated with regional adenopathy. The primary lesion, which may be unnoticed by the patient, resolves within 2 - 6 weeks without any treatment. In untreated individuals, treponemes proliferate in the chancre and are carried via lymphatics to the bloodstream, from which they disseminate throughout the body (1).

The secondary stage of syphilis presents with generalized manifestations on the skin and mucous membranes. It generally appears 4 - 10 weeks after the initial appearance of primary lesion, but in some patients there is an overlap, and a careful examination may disclose a primary chancre (2, 3).

The secondary stage is the most contagious stage of the disease, often presenting with a variety of symptoms, such as malaise, low fever, sore throat, headache, lymph node enlargement, muscle ache in addition to dermatologic manifestations. Known as the great imitator, secondary syphilis may present with a myriad of diverse morphological entities and clinical manifestations (4). This study aimed to describe the clinical characteristics of secondary

syphilis among patients treated at the City Institute for Skin and Venereal Diseases in Belgrade from 2010 to 2014. We also compared HIV-positive and HIV-negative syphilis cases, in order to identify any distinct needs for prevention, screening or other public health measures in these two groups of patients.

Material and Methods

A retrospective chart review of patients with secondary syphilis was undertaken in the City Institute for Skin and Venereal Diseases. Demographic data and data about the possible source of infection, as well as sexual orientation, provided on the official form for notification of syphilis, were also analyzed. The diagnosis of secondary syphilis was based upon the clinical features and positive syphilis serology tests (Venereal Disease Research Laboratory - VDRL and *Treponema Pallidum* Haemagglutination Assay - TPHA).

Data analysis was done using Fisher's exact test. A two-tailed *P* value ≤ 0.05 was considered as significant.

Results

A total of 178 patients were diagnosed with early syphilis (primary, secondary and early latent) at the City Institute for Skin and Venereal Diseases in Belgrade from 2010 to 2014. This study included 62 patients presenting with secondary syphilis. The average patient age was 32 years (range 19 - 59).

The basic socio-demographic characteristics of HIV-negative and HIV-positive patients registered at the City Institute for Skin and Venereal Diseases, Belgrade, in the period 2010 - 2014 are shown in table 1. There were 45 (72.6%) HIV-negative, and 17 (27.4%) HIV-positive patients, with secondary syphilis. The incidence of HIV-positive patients was significantly different from random distribution (p = 0.016). Comparison of basic socio-demographic characteristics (sex, age, marital status and education) between HIV-negative and HIV-positive patients revealed no statistically significant differences. However, all HIV positive cases were men, slightly older and unmarried. A significantly higher percentage of HIV-positive cases were unemployed (p<0.001), reported unknown source of infection (p = 0.002) and were all homosexuals (p = 0.026).

Clinical features of secondary syphilis in patients registered at the City Institute for Skin and Venereal Diseases, Belgrade, in the period 2010 - 2014 are shown in table 2. More than 25% of cases had a history of chancre, which was still present in 11.3% of all patients at the time of examination. The majority of cases (87.1%) had rash (Figures 1 - 4) and lymphadenopathy was found in 20% of patients. All other manifestations were found in a few patients (Figures 5 - 7). However, syphilitic alopecia was detected only in HIV-positive cases (p = 0.004).

Almost all patients with secondary syphilis (80.7%) were treated with 2.4 million units of benzathine penicillin G, in a single dose intramuscularly, except 12 penicillin-allergic patients, who were treated with a 14-day course of oral doxycycline (100 mg twice a day).

Discussion

During the last ten years (2005 – 2014), the incidence of syphilis in Belgrade has been increased by 383.2%, from 1.07 per 100,000 in 2005 to 4.1 per 100,000 in 2014 (5). The first outbreak began in 2010 (6) and culminated in 2014 (5). During these years the disease was more common in males, particularly in men who have sex with men (MSM) and in HIV-infected individuals. In major European cities, several outbreaks of syphilitic infection have been reported among MSM (7, 8, 9).

HIV infection is strongly associated with syphilis, especially among MSM. This association results from the common modes of transmission, but also from the increase of unsafe sexual behavior among HIV-infected MSM (10). Several studies have reported the rate of HIV and syphilis co-infection to be as high as 50% (11-12). According to our results, in the period between 2010 and 2014, more than 25% of syphilitic patients were co-infected with HIV. In our study, when compared with HIV-negative patients, there were significantly more HIV-positive patients with secondary syphilis who were homosexuals, unemployed and had sex with unknown partners. Our results are in accordance with results of other studies, where the majority of HIV-positive syphilitic patients were homosexuals and diagnosed with the secondary stage of disease (13-14). We compared HIV-positive with HIV-negative patients, in order

Table 1. Comparisons of basic socio-demographic characteristics between HIV-negative and HIV-positive patients registered at the City Institute for Skin and Venereal Diseases, Belgrade, 2010 - 2014

Patients	HIV-negative; n (%)	HIV-positive; n (%)	Total; n (%)	*p* value*
Features	45 (72.6)	17 (27.4)	62 (100)	0.016
Sex				
Males	43 (95.5)	17 (100.0)	60 (96.8)	
Females	2 (4.5)	0 (0.0)	2 (3.2)	1.000
Age (years)				
≤ 39	37 (82.2)	13 (76.5)	50 (80.6)	
≥ 40	8 (17.8)	4 (23.5)	12 (19.4)	0.721
Marital status				
Married	3 (6.7)	0 (0.0)	3 (4.8)	
Unmarried	42 (93.3)	17 (100.0)	59 (95.2)	0.555
Education				
≤Elementary	4 (8.9)	0 (0.0)	4 (6.5)	
Secondary/ High	41 (91.1)	17(100.0)	58 (93.5)	0.568
Working status				
Employed	33 (73.3)	3 (17.6)	36 (58.1)	
Other**	12 (26.7)	14 (82.4)	26 (41.9)	<0.001
Employed	33 (86.8)	3 (18.7)	36 (66.7)	
Unemployed	5 (13.2)	13 (81.3)	18 (33.3)	<0.001
Sexual orientation				
Heterosexual	11 (24.4)	0 (0.0)	11 (17.7)	
Homosexual/ bisexual	34 (75.6)	17 (100.0)	51 (82.3)	0.026
Source of infection				
Known	22 (48.9)	1 (5.9)	23 (37.1)	
Unknown	23 (51.1)	16 (94.1)	39 (62.9)	0.002

n, number of patients; *, according to Fisher's exact test; **, unemployed plus supported and retired persons; *p* value ≤ 0.05 was considered as significant

Table 2. Clinical features of secondary syphilis among patients registered at the City Institute for Skin and Venereal Diseases, Belgrade, 2010 - 2014

Clinical features	n (%)
History of chancre	17 (27.4)
Chancre still present	7 (11.3)
Rash	54 (87.1)
Lymphadenopathy	12 (19.4)
Fever/malaise	3 (4.8)
Condylomata lata	2 (3.2)
Alopecia	4 (6.4)
Mucous patch	4 (6.4)

n, number of patients

to determine whether there were distinct needs for prevention, screening or other public health measures in these two groups of patients. Remarkably, 86.8% of HIV-positive and 18.7% of HIV-negative cases were unemployed. People who struggle financially often experience life circumstances, which increase their risks for sexually transmitted infections (15).

During the first stage of syphilis, clinical manifestations of syphilitic infection are usually confined to the local site of inoculation, and about 25% of patients with untreated infection develop secondary syphilis within 4 to 10 weeks after the primary lesion (3). In our study, 27.4% of cases had a history of primary lesion, but they ignored it or were mistreated by their physicians (16). However, not all of the infected patients have a history of a preceding chancre, since it may have gone unnoticed (e.g. oral, rectal or vaginal lesions). The chancre heals within 2 - 6 weeks, and lymphadenopathy usually persists longer. The symptoms and signs of secondary syphilis often develop while the chancre is still present, especially in HIV-infected patients (13, 17). According to our results, in 7 (11.3 %) patients with secondary syphilis chancre was still present and the majority of these patients (57.1%) were HIV-positive. Lesions of secondary syphilis result from the hematogenous dissemination of *treponemes* from syphilitic chancres.

An extremely broad spectrum of skin and mucosal lesions are seen in patients with secondary syphilis. Generalized clinical symptoms and signs occur during this stage, e.g. fatigue, weakness, headache, myalgia, arthralgia, generalized lymphadenopathy, which may affect almost any system of organs (18). Hepatitis (subclinical), meningitis, iridocyclitis, anterior uveitis, arthritis and glomerulonephritis also occur in the second stage (1). Secondary syphilis typically resolves spontaneously after 3 to 12 weeks, although about 25% of untreated individuals have a relapse during the first year (4). The earliest visible lesions are pale pink or reddish macules usually 4 to 8 mm in diameter on the patient's body and limbs, as in our patients (Figure 1). This eruption, called *roseola syphilitica,* is asymptomatic and never appears on the face, in contrast to all other types of syphilitic lesions; it is transitory, generally lasting for a few days, and it is frequently overlooked or misdiagnosed (4). This rash may change into, or be followed by a symmetric nonpruritic most frequently papular exanthema present in more than 87% of our patients, involving the entire trunk and extremities including palms

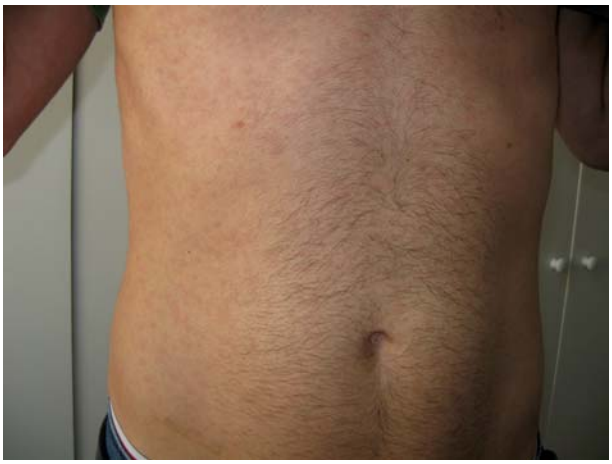

Figure 1. Roseola syphilitica with pale pink macular lesions on the trunk

and soles. Papular lesions may have several different morphologic variants (Figures 2 - 4), such as small or large, follicular, papulosquamous (psoriasiform or lichenoid appearance), corymbiform, annular, pustular, rupial and frambesiform papules (4).

Moist papular lesions, also known as condylomata lata, present in two of our patients, may appear in two different forms; the first includes flat moist papules, and the second elevated verrucous or cauliflower-like papules. These lesions are predominantly found in the anogenital region (Figure 5), but may occur in other intertriginous areas (between the toes, fingers and axilla).

Long lasting postinflammatory hyperpigmentations or hypopigmentations may also occur in secondary syphilis, like small patches around the patient's neck, the so called neklace of Venus (18).

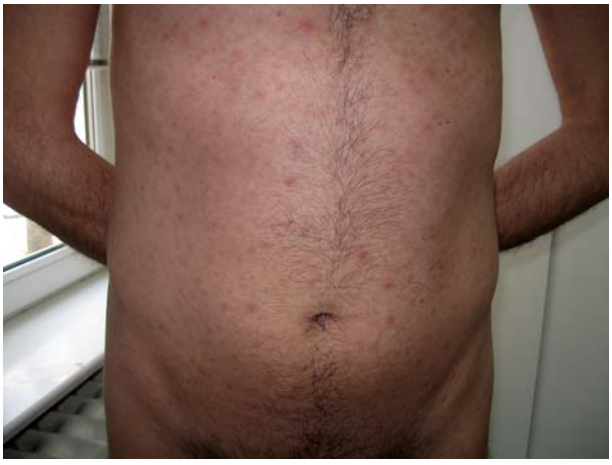

Figure 2. Maculopapular rash in secondary syphilis

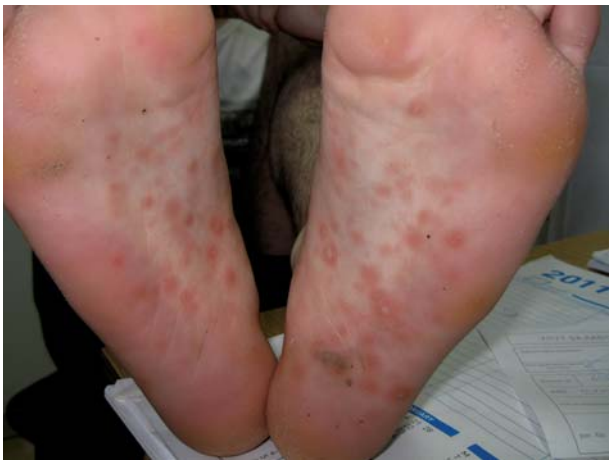

Figure 3. Characteristics papulosquamous lesions of secondary syphilis on the soles

Scalp involvement in secondary syphilis leads to alopecia. In our study it significantly affected only HIV-positive patients. Syphilitic hair loss presents as areolar alopecia, patchy "moth-eaten" thinning occurring in small irregular areas (Figure 6), and rarely as a diffuse telogen effluvium. Loss of eyelashes and lateral third of the eyebrows also occur in the second stage of the disease (18).

There are two principal lesions that affect the oral mucous membrane in secondary syphilis; flat-to-slightly raised red macular lesions on the hard palate, and oval or serpiginous often erosive or even ulcerating mucous patches most frequently seen on mobile oral mucosal surfaces; the latter were detected in 6.4% of our patients (Figure 7).

The differential diagnosis of secondary syphilis includes a variety of different conditions. Cutaneous

Figure 4. Annular psoriasiform plaques on the penile shaft in a HIV-infected patient

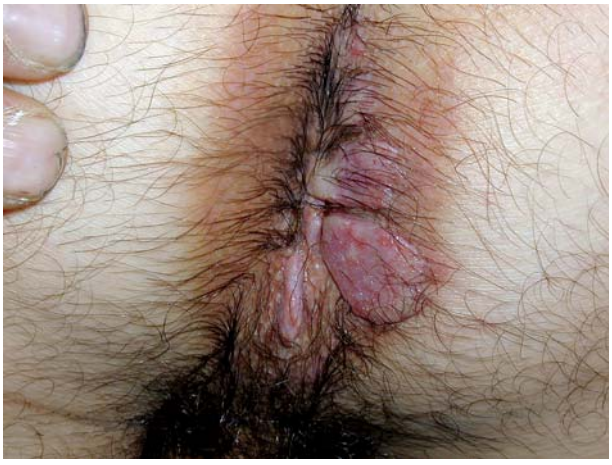

Figure 5. Perianal condylomata lata

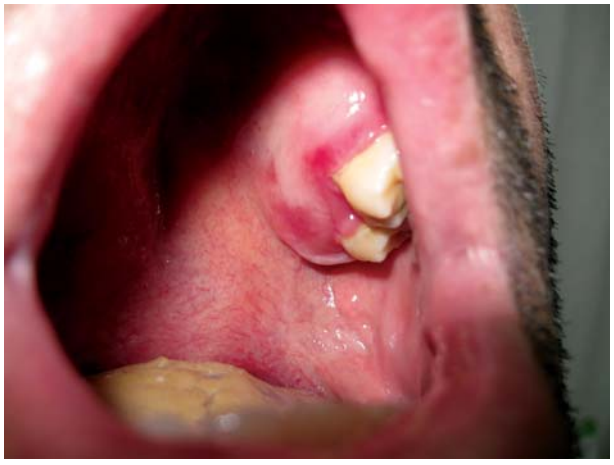

Figure 7. Mucous patch in the oral cavity

manifestations of secondary syphilis may mimic a variety of dermatological diseases including pityriasis rosea, psoriasis, drug-induced eruptions, sarcoidosis, viral exanthema, pityriasis lichenoides chronica and lichenoid eruptions (1, 18). The presence of palmoplantar involvement is an important distinguishing feature of secondary syphilis. Condylomata lata may be confused with anogenital warts, Bowen's disease and Bowenoid papulosis (1, 18). Clinical conditions that mimic "moth-eaten" syphilitic alopecia include alopecia areata, alopecia neoplastica, tinea capitis and trichotillomania, while diffuse syphilitic alopecia must be distinguished from telogen effluvium of other etiology and androgenetic alopecia (18).

The diagnosis of secondary syphilis is routinely established by medical history, clinical presentation and is confirmed, like in our study, by serologic testing. Serologic tests for syphilis, treponemal (TPHA), as well as nontreponemal (VDRL), are uniformly positive in the secondary stage of the disease, with the exception of false-negative VDRL test, that may occur in secondary syphilis due to prozone phenomenon, if undiluted serum is used (19). Although dark-field microscopy is actually the only test that specifically establishes the diagnosis of secondary syphilis, it is not recommended in non-erosive or non-ulcerating samples, particularly if located in the oral cavity (1).

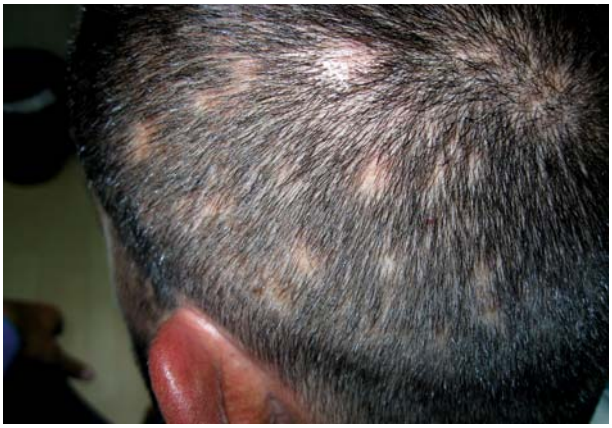

Figure 6. Alopecia in secondary syphilis with a patchy, diffuse and „moth-eaten" appearance in a HIV-infected patient

All of our patients were successfully treated with a single intramuscular injection of benzathine penicillin, or with a 2-week regimen of doxycycline. The non-treponemal antibody test titres correlate with the disease activity, and usually become negative with time after successful treatment. The treponemal antibody tests remain positive after successful treatment (18). In our patients successful treatment was confirmed by a fourfold decrease in pretreatment VDRL titres at 6 - 12 months follow-up.

Contact tracing of sexual partners and their treatment is an important control measure for syphilis. As described in our study, significantly more HIV-infected patients had sex with unknown partners and contact tracing was not effective. For patients with secondary syphilis, sexual partners within the past six months should be notified, moreover, for patients with clinical relapses, partner notification may have to be extend to two years (20).

An impressive spectrum of cutaneous manifestations of secondary syphilis emphasizes the

importance of dermatological education of non-experienced physicians, particularly in current circumstances with syphilis resurgence in Serbia.

Conclusion

Clinicians must maintain a high index of suspicion, especially when assessing vulnerable populations, such as men who have sex with men and HIV-infected individuals. Counseling for sexually transmitted diseases, should be offered to all patients visiting dermatologists, and it should be stressed that risky behavior may also result in the transmission of HIV.

Acknowledgement

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Abbreviations

HIV – human immunodefi ciency virus
VDRL – Venereal Disease Research Laboratory
TPHA - *Treponema Pallidum* Haemagglutination Assay
MSM - men who have sex with men

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Sekundarni stadijum sifilisa kod pacijenata koji su lečeni u Gradskom zavodu za kožne i venerične bolesti u Beogradu u periodu 2010–2014. godine

Sažetak

Uvod. S obzirom na to da je sifilis poznat kao veliki imitator, u radu se navode dermatološka oboljenja koja su značajna u diferencijalnoj dijagnozi sekundarnog stadijuma ove bolesti.

Cilj ovog rada je analiza karakteristika i kliničkih manifestacija sekundarnog sifilisa kod obolelih koji su registrovani u Gradskom zavodu za kožne i venerične bolesti u Beogradu u periodu od 2010. do 2014. godine.

Rezultati. U radu su prikazana 62 pacijenta sa sekundarnim sifilisom. Prosečna starost obolelih bila je 32 godine. Od pacijenta sa sekundarnim sifilisom, njih 45 (72,6%) bilo je HIV negativno, a 17 (27,4%) HIV pozitivno. Broj HIV pozitivnih pacijenata sa sifilisom se značajno razlikovao od slučajnog (p = 0,016). Svi HIV pozitivni pacijenti bili su neoženjeni muškarci, nešto stariji od HIV negativnih obolelih, a značajno su se razlikovali od njih po tome što su svi bili homoseksualne orijentacije (p = 0,026); veći broj je bio nezaposlen (p < 0,001) i značajno veći broj među njima je sifilis dobio tokom seksualnog odnosa sa nepoznatim partnerom (p = 0,002).

Više od četvrtine od svih obolelih je dalo podatak o primarnom šankru u ličnoj anamnezi, a šankr je prilikom pregleda dijagnostikovan kod 11,3% svih pacijenata. Ospa karakteristična za sifilis bila je prisutna kod 87,1% pacijenata, a limfadenopatija je dijagnostikovana kod 20% obolelih. Sifilitična alopecija je detektovana samo u grupi HIV pozitivnih pacijenata (p = 0,004). Ostale manifestacije sekundarnog sifilisa poput mukoznih plakova, alopecije i *condylomata lata* registrovane su kod manjeg broja obolelih a razlike u njihovoj učestalosti između HIV pozitivnih i HIV negativnih pacijenata nisu dostigle statistički značaj.

Zaključak. Lekari praktičari uvek moraju da uključe u diferencijalnu dijagnozu veliki broj dermatoza i dijagnozu sekundarnog sifilisa, naročito kod vulnerabilne populacije – poput muškaraca koji imaju seksualne odnose sa muškarcima i pacijenata inficiranih HIV-om.

Ključne reči

Sifilis; Kutani sifilis; Dijagnoza; Seksualno prenosive bolesti; Homoseksualnost kod muškaraca; HIV infekcije; Znaci i simptomi

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Yellow Nail Syndrome - a Case Report

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UDK 616.596:616.2-036.1]-08

Abstract

Yellow nail syndrome is a rare disease of unknown etiology. It is clinically characterized by a triad of yellow nails, lymphedema at one or more sites, and chronic respiratory disease (bronchitis, bronchiectasis and rhinosinusitis). All nails may be affected, but some may be spared. The nail plates are yellowish green, thickened, occasionally with transverse ridging and onycholysis, with increased longitudinal and transversal over-curvature, with partial or complete separation of the nail plate from the nail bed, without lunula and cuticle and slow nail growth rate. The lymphedema is usually peripheral, affecting the lower limbs, or in the form of pleural effusion.

This is a case report of a 47-year-old female patient who presented with nail changes at the age of 40; two years later the patient developed lymphedema of the lower limbs, and a year later a chronic respiratory disease. The affected nails were yellow to yellow-gray, with thickened nail plates separated from the nail bed, ingrown in the perionychium, without lunula. At the same time, additional examinations revealed the following associated conditions: edema of talocrural joints in both legs, chronic obstructive bronchitis, bronchial asthma, chronic rhinitis with bilateral nasal polyposis, labile arterial hypertension. Apart from the management of chronic respiratory disease, oral vitamin E capsules (200 mg 3 times a day) and topical vitamin E solution were administered over 15 months. The nails began to grow, and the newly grown nails were of normal pigmentation.

In conclusion, we present a case of an adult female patient with yellow nail syndrome, and a recognized association of peripheral edema and chronic pulmonary disease. The patient had a typical clinical picture, all the nails were affected, but showed a favorable response to systemic and topical vitamin E therapy.

Key words

Yellow Nail Syndrome; Lymphedema; Bronchitis, Chronic; Asthma; Vitamin E; Treatment Outcome; Case Reports

Yellow nail syndrome (YNS) is a rare disease of unknown etiology (1). The term YNS was first described by Samman and White in 1964 (2). They reported a group of 13 patients with lymphedema of the lower extremities and yellow nails. In 1966 (3), Emerson described a patient with a pleural effusion. All nails may be affected, but some may be spared (4). Although there are data claiming that only two groups of symptoms appear in 1/3 of cases (3), the typical clinical picture of YNS (5, 6) is characterized by a triad of yellow nails, lymphedema at one or more sites, and chronic respiratory disease (bronchitis, bronchiectasis and rhinosinusitis) (7 - 12).

The disorder is characterized by discoloration of nail plates which varies from light brown, dark yellow, yellow and green, with thickening, occasionally with transverse ridging and onycholysis, increased longitudinal and transversal over-curvature, partial or complete separation of the nail plate from the nail bed, without lunula and cuticle, with slow nail growth rate (13 – 16).

The lymphedema is mostly peripheral (lower limbs or hands), or affects the face, larynx, with pleural effusion and ascites, and occasionally it is universal (17). In some cases the edema has been shown to be due to abnormalities of the lymphatics, either atresia

or varicosity. Other cases have normal lymphatics, indicating that a functional rather than an anatomical defect may be present, or only the smallest lymph vessels are defective (4).

Respiratory disorders include: sinusitis, recurrent pneumonia, chronic bronchitis, bronchiectasis, pleural effusion (18).

It is believed that YNS is caused by lymphatic abnormalities, either anatomical (found only in a minority of patients with congenital abnormalities), or functional, with increased microvascular permeability (19). A dense fibrous tissue has been found in the nail bed and matrix, replacing subungual stroma with scattered ectatic vessels; obstruction of lymphatics by this dense stroma may be responsible for the abnormal lymphatic function found in the affected digits in some but not all cases (4). Reduced lymphatic drainage may cause peripheral edema or pleural effusion (13, 16).

Case report

The case history of a 47-year-old female textile worker shows that she presented with nail changes at the age of 40. Her nails stopped growing and became dark in color. Antifungal therapy provided some improvement. Two years later, at the age of 42, she had pneumonia and since the age of 43 she suffers from chronic obstructive bronchitis. She also developed edema of both legs, expressed especially in the morning, followed by numbness of fingers. Since the age of 45, in the last two years, all her nails have been discolored, yellow to yellow-gray, thickened, ingrown, painful, and almost stopped growing. Due to leg edema she was treated at the Institute of Rheumatology in Belgrade with the diagnosis: polyarthralgia and edema of talocrural joints of both legs. Her family history was negative.

Physical examination

Skin examination showed yellowish to gray nails; the nail plates were thickened, separated from the nail bed, without lunula and cuticle, laterally ingrown in the perionychium (tweezer look), accompanied by pain (Figures 1 and 2). Lower extremities, ankles and feet were affected with edema: elastic edema, without skin discoloration (Figure 3).

Laboratory and other test results

The relevant laboratory test results were within reference values.

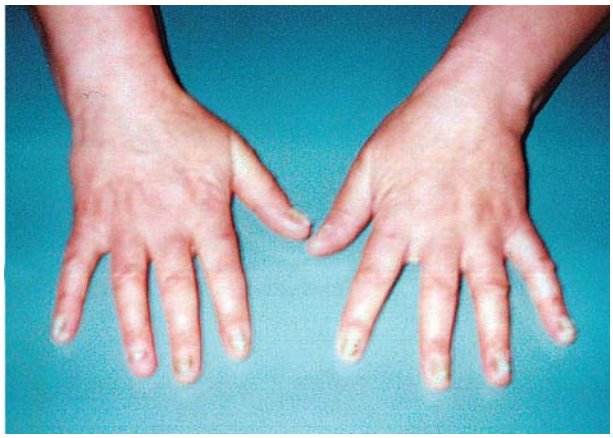

Figure 1. Prior therapy: fingernails are yellow to yellowish-gray, nail plates are thickened, separated from the nail bed, without lunula

Color Duplex Doppler ultrasound findings of the lower limb veins and arteries were within the normal range.

Chest and heart X-ray: slightly prominent bilateral hilar-basal shadows; the cardiac silhouette was normal in size and contour.

Spirometry - spirogram: mild obstructive pulmonary insufficiency.

Bronchial provocation test with methacholine: negative.

Pulmonary perfusion scintigraphy: no clear scintigraphic signs of perfusion abnormalities.

Skin prick testing to aeroallergens: positive to grass pollen and textile dust.

Pulmonary findings - diagnosis: chronic obstructive bronchitis, bronchial asthma.

ENT findings - diagnosis: chronic rhinitis,

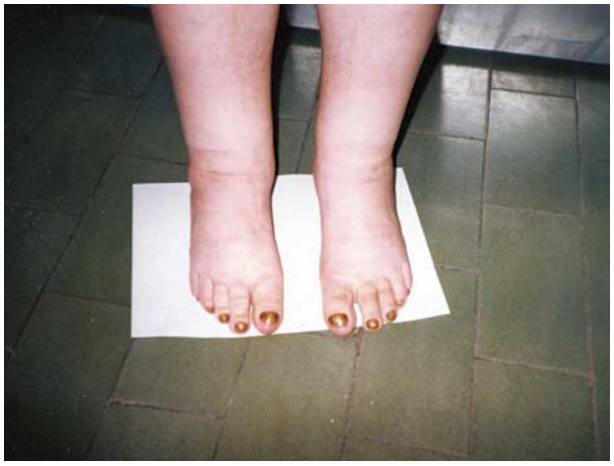

Figure 2. Prior therapy: nail plates of toenails are dark yellow and thickened

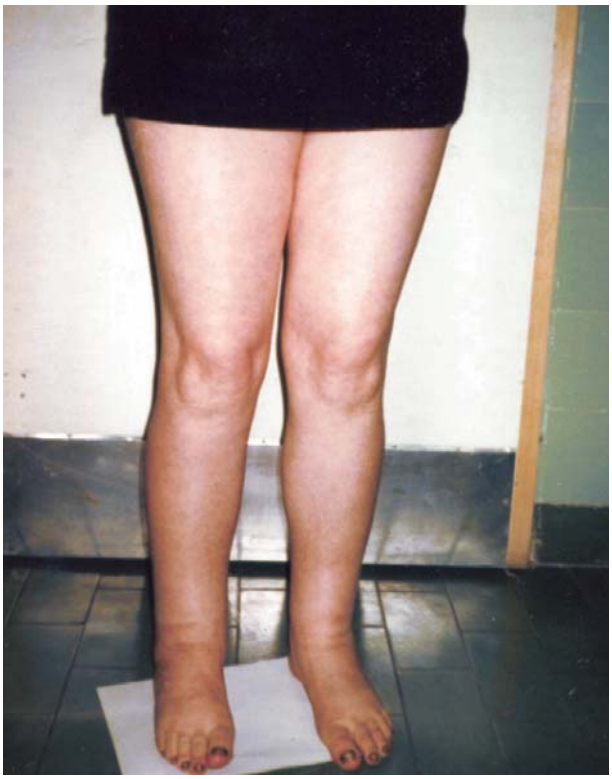

Figure 3. Prior therapy: edema of the lower legs, ankles and feet

bilateral nasal polyposis, bilateral cochlear nerve lesions.

Ophthalmology findings - diagnosis: traumatic cataract of the left eye, concomitant strabismus.

Cardiovascular examination - diagnosis: labile arterial hypertension.

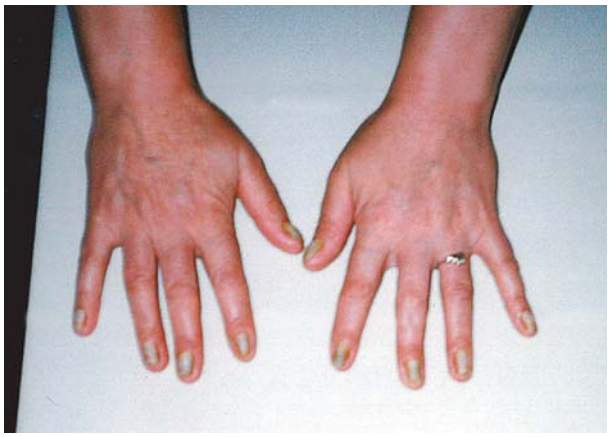

Figure 4. After 15 months of therapy: nail plates of fingernails with discoloration, separated from the nail bed, yellowish in the distal parts, the proximal parts of normal appearance

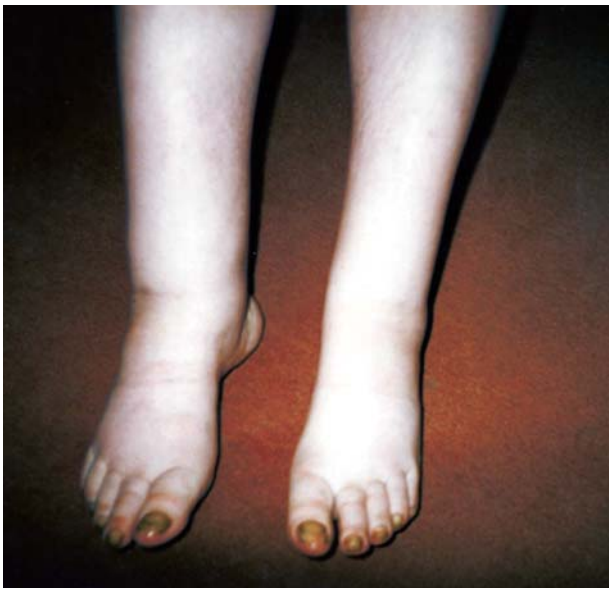

Figure 5. After 15 months of therapy: nail plates of toenails are thickened, yellowish-brown in the distal parts

Therapy

In addition to the medications prescribed by the pulmologist and cardiologist, vitamin E capsules (200 mg 3 times a day), topical vitamin E solution, and AD drops were initiated. Several months later, the treatment showed improvement: the nails started growing, the

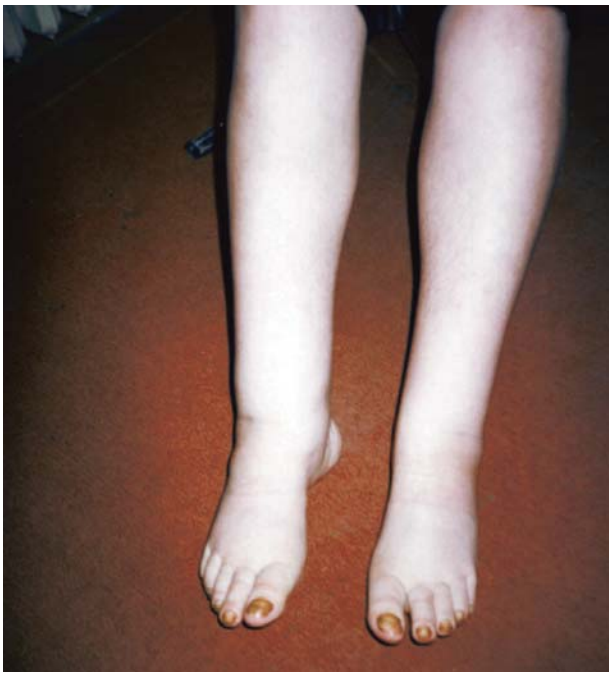

Figure 6. After 15 months of therapy: lower legs, ankles and feet are swollen, affected by lymphedema

proximal parts of nail plates were of normal color, and the lunula became visible.

On follow-up examination, after 15 months of treatment, the nail plates on the hands were yellowish in the distal portion, from 1 to several millimeters (Figure 4). The toenail plates were thickened, yellowish-brown in the distal portion, from 1mm to involvement of the whole thumb nail plate; the proximal nail plates were normal (Figure 5); the lower legs, ankles and feet were swollen, affected by lymphedema (Figure 6).

Discussion

According to the literature data, up to 2004, there were 150 case reports on YNS (17), by 2014, about 200 cases were described (1), confirming that it is an extremely rare disease.

The syndrome affects all age groups: from birth to old age (20, 21, 22): Valdés et al. reviewed reports on 150 patients aged 0 to 88 years, with a median age of 60 years (range from 41 to 80 years) (12). The literature data show that the disorder is more common in females, with a female to male ration of 1.6 : 1 (10, 23, 24). In their study, Valdés et al. reported a male to female ratio of 1.2 : 1 (12). According to the world literature, only a small number of reports have been published on YNS in children (8, 25 - 28); congenital cases have been reported as well (28, 29).

According to Valdés and associates (12), lymphedema was observed in all patients, nail discoloration in 85.6%, and pleural effusion in 68.3%, while other authors claim that nail discoloration was registered in 89% of patients, lymphedema in 80%, and respiratory disease in a 63% (25, 28, 30). There is a case report of a girl with lymphedema and pleural effusion, without nail discoloration (8), a boy only with nail discoloration (28), and a female patient who had yellow nails since childhood, without lymphedema, who postpartum developed a massive pleural effusion (21). Our patient exhibited a clinical triad of nail discoloration, lymphedema, and a respiratory disease. Nail discolorations may precede other symptoms, as in our case, may appear at the same time, or later (14). All nails are affected only in 10% of cases (9). The nail growth is always slow, 0.1 to 0.25 mm per week, instead of 0.5 to 2 mm per week (4, 14). In our patient nail discoloration started before other manifestations of the triad, but it fully developed later.

There are opinions that YNS is a hereditary disorder, transmitted in an autosomal dominant fashion (31). Although congenital hypoplasia of the lymphatics plays an important role in the clinical picture (10), in a series of 150 patients (12), familial YNS was registered only in 9 patients. Due to low incidence of familial cases (32), it has generally been accepted that YNS is not primarily a genetic, but a sporadic (20), acquired disorder (16). It may be idiopathic or secondary to systemic diseases, or a result of adverse drug effects (6, 33). The pathology of YNS is not known (28). Firstly, hypoplastic or deficient lymphatic vessels have been postulated as the cause; it has been hypothesized that the clinical manifestations of YNS are the result of primary stromal sclerosis, which may lead to lymphatic obstruction. Lymphangiography has demonstrated anatomic defects in both the number and size of the lymphatic vasculature of some, but not all patients, as mentioned before. The reversibility of YNS and the lack of demonstrable anatomic defects in some patients suggest that the underlying cause of this condition may be a functional rather than an anatomic abnormality. It is assumed that the respiratory component of the disease is caused either by lymphatic system hypoplasia or the immune deficiency (34). YNS can be associated with combined immune deficiency, which may be responsible for associated sinopulmonary infections manifestations (20).

YNS has been associated with a variety of diseases (17). The most common conditions associated with YNS include malignant diseases - melanoma (3), bronchogenic carcinoma (35), thoracic carcinoma (36) renal cell carcinoma (37); lymphproliferative diseases (38, 39); immune deficiency conditions (39), acquired immunodeficiency syndrome (40); endocrine diseases (25, 40, 41, 42); connective tissue diseases (10, 43, 44); obstructive sleep apnea (45); xanthogranulomatous pyelonephritis (46), nephrotic syndrome (47), membranous glomerulonephritis (24), tuberculosis (48) post-myocardial infarction (49), pericardial effusion (50), asthma (42). YNS has been reported after treatment with sodium valproate, D-penicillamine (51), and gold sodium thiomalate in the treatment of rheumatoid arthritis (52).

Valdés and associates (12) studied reports of 150 patients, out of which 14 presented with malignancy. There are opinions that YNS should be examined in terms of neoplasia (52), even some claiming that it is a paraneoplastic disease (53).

Clues to diagnosis are the presence of dystrophic, yellowish nails, peripheral lymphedema and pleural effusions (54). Nail changes are of greatest diagnostic significance; they should be distinguished from changes found in lichen planus, which is not associated with systemic symptoms, whereas changes on the nail plates are characteristically followed by atrophy (especially visible on the nails on the hands), which is not the case in YNS (4). Some authors believe that the appearance of yellow nails in hypothyroidism and in acquired immune deficiency syndrome (AIDS) is solely the result of slow nail growth (40). Differential diagnosis should include systemic edemas, as well as long-term pleural effusions in patients with bronchiectasis and sinusitis (54).

Apart from adequate treatment of recurrent infections, pleural effusion and associated diseases, André (55) recommends the following treatment of nail changes: intradermal triamcinolone acetonide injections, topical application of vitamin E in DMSO (dimethyl sulphoxide), oral vitamin E - 400 - 800 IU/day during 18 months, and zinc sulphate - 300 mg/day for 2 years, in combination with antimycotics, if necessary (55). Itraconazole increases the longitudinal growth rate of nail plates (4). The combination of vitamin E and antimycotics, (itraconazole or fluconazole) in secondary infection, has led to significant improvement. Douri (29) also reported about beneficial effects of vitamin E in the treatment of this disorder. After 6 months of treatment with vitamin E solution, Lambert reported an improvement of fingernail growth rate, but not significant compared to placebo (28). The assumed mechanisms of favorable effects of vitamin E are based on its antioxidant effects in vivo, which play an important role in cell membranes protection from oxidative damage by free radicals, in blocking the production of yellow pigment lipofuscin (pigment resulting from lipid oxidation of free radicals, causing different degrees of yellow color in tissues) and in prevention of the DNA and other cellular proteins damage, which may disturb the keratinization process and decrease the growth rate of nails (56).

Our patient presented with a classic triad of YNS: yellow nails, lymphedema and respiratory disorders. The first changes appeared on the nails, then respiratory disorders, and finally lymphedema. After consulting a pulmonologist, she received treatment for respiratory problems. Topical and oral vitamin E therapy resulted in improvement in terms of nail growth rate without yellow discoloration.

The course of the disease is generally benign, and clinical manifestations are usually managed with the above mentioned therapy (17). Spontaneous improvement of nail discoloration is reported in up to 30% of cases (6, 46).

Conclusion

We report a rare case of yellow nail syndrome where all the nails were affected, with a recognized association with chronic pulmonary disease and edema of the legs, and favorable response to systemic and topical vitamin E treatment.

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Sindrom žutih noktiju – prikaz slučaja

Sažetak

Uvod. *Yellow nail* syndrom (YNS), sindrom žutih noktiju, retka je bolest nerazjašnjene etiologije. Nokti mogu biti zahvaćeni svi ili samo pojedini. Iako postoji podatak da 1/3 bolesnika ima samo dve komponente sindroma, klasična klinička slika YNS opisuje se kao trijada koju karakterišu: žuti nokti, limfedem na jednom ili više mesta i hronična respiratorna bolest (bronhitis, bronhiektazije, rinosinuzitis). Limfedem može biti periferan (donji udovi ili šake), ili facijalan, laringealan, u vidu pleuralne efuzije i ascitesa, retko univerzalan: respiratorni poremećaji: sinuzitis, rekurentne pneumonije, hronični bronhitis, bronhiektazije, pleuralna efuzija.

Smatra se da YNS nastaje usled limfatične abnormalnosti, bilo anatomske (utvrđene samo kod malog broja obolelih koji su imali kongenitalne abnormalnosti) ili funkcionalne – sa povećanom mikrovaskularnom permeabilnošću. Redukovana limfna drenaža može izazvati periferni edem ili pleuralnu efuziju.

Prikaz slučaja. Ženska osoba stara 47 godina, po zanimanju tekstilna radnica, izjavila je u anamnezi da su joj se prve promene na noktima javile u 40. godini života. Nokti su prestali da rastu, postali tamnije prebojeni. Pod terapijom antimikoticima došlo je navodno do poboljšanja. Dve godine kasnije, u 42. godini, imala je upalu pluća a od 43. godine života hronični opstruktivni bronhitis. Od tada se razvio edem obeju nogu, izražen naročito ujutro, praćen trnjenjem prstiju. Od njene 45. godine, poslednje dve godine, svi nokti su postali izmenjene boje, žuti do žutosivi, zadebljali, uraslih ivica, bolni; pacijentkinja ima utisak da ne rastu. Zbog otoka nogu lečena je na Institutu za reumatologiju u Beogradu pod dijagnozom: poliartralgija i obostrani edem talokruralnih zglobova. U porodici nije bilo obolelih srodnika. Prilikom dermatološkog pregleda uočeno je da su svi nokti (i na rukama i na nogama) intenzivno žuto do žućkastosivo prebojeni, nokatne ploče zadebljale, odignute, bez lunule i kutikule, lateralne strane urasle u perionihijum (izgled pincete), što je bilo praćeno bolom (slike 1 i 2). Potkolenice, skočni zglobovi i stopala bili su edematozni: edem elastičan, boja kože neizmenjena (Slika 3).

Relevantne laboratorijske analize bile su u granicama referentnih vrednosti. Kolorni dopler dupleks ultrazvučni pregled vena i arterija donjih ekstremiteta, rendgenski snimak pluća i srca, kao i perfuziona scintigrafija pluća bili su u referalnim granicama. Spirometrijom je utvrđena laka opstruktivna insuficijencija plućne ventilacije. Bronhoprovokativni test sa metaholinom je bio negativan. Alergološkim testom uboda utvrđena je preosetljivost na polen trava i tekstilnu prašinu. Pulmolog je na osnovu sprovedenih ispitivanja postavio dijagnozu hroničnog opstruktivnog bronhitisa i bronhijalne astme, a specijalista za bolesti uva, grla i nosa, utvrdio je kod pacijentkinje prisustvo hroničnog rinitisa i bilateralne nazalne polipoze.

Terapija je ciljano podrazumevala vitamin E u vidu kapsula u dozi od 200 mg triput dnevno, i u vidu aplikacije rastvora vitamina E i AD u ulju. Posle nekoliko meseci lečenja, došlo je do poboljšanja tako što su nokti počeli da rastu; proksimalni delovi nokatnih ploča dobili su normalnu boju; lunula je postala vidljiva. Nokatne ploče ruku i nogu su na kontrolnom pregledu, obavljenom posle 15 meseci primene terapije, bile žućkasto prebojene u distalnim delovima, dok su proksimalni delovi nokatnih ploča bili normalnog izgleda i boje (slike 4 i 5); potkolenice, skočni zglobovi i stopala su bili uvećanog obima zbog limfedema (Slika 6).

Diskusija. Do 2004. godine, opisano je 150 slučajeva sindroma žutih noktiju, do 2014. oko 200 slučajeva, što potvrđuje navod da se bolest retko javlja. Sindrom može početi u periodu od rođenja do kasnog životnog doba. U literaturi se navode podaci da se bolest češće javlja kod žena, te da je odnos polova 1,6 : 1 u korist žena, dok su rezultati pojedinih autora ukazali na odnos polova 1,2 : 1 u korist muškaraca. U svetskoj literaturi objavljen je samo mali broj slučajeva sindroma kod dece; opisana je i kongenitalna pojava bolesti.

U ispitivanjima novijeg datuma, limfedem je registrovan kod svih bolesnika, promene na noktima kod 85,6%, a pleuralna efuzija u 68,3%, dok su u

ispitivanjima drugih autora promene na noktima registrovane kod 89% bolesnika, limfedem kod 80%, a respiratorne bolesti kod 63%. U literaturi je objavljen slučaj devojčice koja je imala limfedem i pleuralnu efuziju bez promena na noktima, dečaka samo sa promenama na noktima kao i bolesnice koja je od detinjstva imala žute nokte bez limfedema, a post partum je nastala masivna pleuralna efuzija.

Naša pacijentkinja je imala klasičnu trijadu, promene na noktima, limfedem i respiratornu bolest. Promene na noktima inače mogu da prethode drugim simptomima, kao u našem slučaju, ili da se javljaju istovremeno, ili kasnije. Svi nokti su zahvaćeni u samo 10% slučajeva, a rast noktiju je usporen. Kod naše bolesnice su promene na noktima počele pre drugih manifestacija trijade, ali su se kompletno razvile kasnije.

U patogenezi oboljenja, postoje stavovi da je sindrom žutih noktiju nasledna bolest, sa autozomno dominantnim načinom nasleđivanja. Zbog retkih familijarnih slučajeva, prihvaćena je hipoteza da to nije primarno genetska bolest, već da je stečeno oboljenje. Može biti idiopatska ili sekundarna u okviru sistemskih bolesti, ili posledica neželjenih efekata lekova. Pretpostavka je da su hipoplastični ili deficijentni limfatični sudovi uzrok sindroma žutih noktiju; postji i hipoteza da su kliničke manifestacije rezultat primarne stromalne skleroze, a njen rezultat može biti limfna opstrukcija. Limfangiografija je demonstrirala anatomski defekt u broju i veličini limfatične vaskulature kod nekih, ali ne svih pacijenata, kako je već ranije navedeno. Reverzibilnost sindroma žutih noktiju i nedostatak demonstriranja anatomskih defekata kod svakog pacijenta ukazuju na to da se pre može raditi o funkcionalnoj nego anatomskoj malformaciji. Pretpostavlja se da je respiratorna komponenta bolesti izazvana ili hipoplazijom limfnog sistema ili imunodeficijencijom. Kombinovana imunodeficijencija može biti odgovorna za manifestaciju udružene sinopulmonalne infekcije. Opisana je udruženost sindroma žutih noktiju sa mnogim bolestima: maligne bolesti limfoprliferativne bolesti; imunodeficijentna stanja, sindrom stečene imunodeficijencije; endokrine bolesti; bolesti vezivnog tkiva; pijelonefritis, nefrotski sindrom. tuberkuloza, miokardni infarkt, perikardna efuzija, astma. Takođe je zabeležena pojava sindroma žutih noktiju posle primene natrijum-valproata, penicilinamina D i soli zlata. Sindrom žutih noktiju je za pojedine autore paraneoplazijski sindrom.

Dijagnoza se postavlja na osnovu kliničke slike, i to prisustva najmanje dva od tri osnovna kriterijuma: promene na noktima, limfedem i pleuralna efuzija. Najveći dijagnostički značaj ima prisustvo promena na noktima; njih treba razlikovati od promena u okviru oboljenja lihen planus kod koga nema sistemskih promena, a lokalnim nalazom dominiraju promene na površini nokatnih ploča i atrofija (naročito vidljiva na noktima na rukama), koja nije prisutna u sindromu žutih noktiju. Pojavu žutih noktiju u hipotiroidizmu i kod osoba sa sidom (AIDS – eng. *acquired immune deficiency syndrome*) neki smatraju isključivo posledicom usporenog rasta nokatne ploče. Diferencijalno-dijagnostički treba razlikovati sistemske edeme, kao i dugotrajne pleuralne efuzije kod pacijenata sa bronhiektazijama i sinuzitisom.

U lečenju promena na noktima, preporučuje se: intradermalno unošenje triamcinolon acetonida, lokalna aplikacija vitamina E u DMSO (*dimethyl sulphoxide*), oralno vitamin E u dnevnoj dozi od 400 do 800 internacionalnih jedinica u toku 18 meseci i oralno cink-sulfat u dozi od 300 mg/dan u toku dve godine, po potrebi u kombinaciji sa antimikoticima. Itrakonazol ubrzava longitudinalni rast nokatnih ploča. Pretpostavljeni mehanizam povoljnog dejstva vitamina E zasniva se na njegovim antioksidantnim mogućnostima *in vivo.*

Tok oboljenja je generalno benigan i primenjenom terapijom mogu da se kontrolišu kliničke manifestacije. U pojedinim slučajevima, čak kod 30% pacijenata, može doći i do spontanog izlečenja.

Zaključak. Prikazan je slučaj retkog sindroma žutih noktiju u kome su svi nokti bili zahvaćeni uz prisustvo hroničnog opstruktivnog oboljenja pluća i edema obe potkolenice i povoljnim dgovorom na sistemsku i lokalnu terapiju vitaminom E.

Ključne reči: Sindrom žutih noktiju; Limfedem; Hronični bronhitis; Astma; Vitamin E; Ishod lečenja; Prikazi slučajeva

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Periungual Pyogenic Granuloma-Like Lesions During Isotretinoin Treatment for Acne: Two Case Reports and a Literature Review

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Abstract

Periungual pyogenic granuloma-like lesions are not uncommon side effects of isotretinoin therapy, but these cases are relatively infrequently reported. Excessive granulation tissue appeared in two patients receiving oral isotretinoin therapy for severe acne. Once isotretinoin was discontinued, the outgrowths resolved spontaneously in both patients. It is probably an idiosyncratic reaction to isotretinoin which renders the skin more susceptible to extracellular matrix and blood vessel formation. Moreover, similar lesions may be observed particularly with newer targeted therapies, such as inhibitors of epidermal growth factor receptor (EGFR) and mitogen-activated protein kinase kinases (MEKs). EGFR inhibitors associated painful periungual inflammation (paronychia), which often arises from the nail wall during newer targeted therapies, has been classified in the third major group of dermatologic toxicity. Cutaneous toxicity may be interpreted as a stress response that affects epidermal homeostasis. In the cell, stress signals are transmitted to effectors which then produce an inflammatory response.
In conclusion, paronychia and excessive granulation tissue in the nail folds are not uncommon side effects of oral retinoids. It is therefore particularly important for practicing dermatologists to be aware that the best management approach is drug discontinuation.

Key words

Granuloma, Pyogenic; Nail Diseases; Isotretinoin + adverse effects; Acne Vulgaris; Case Reports; Review

Isotretinoin (13-*cis* retinoic acid) is a well established and the most effective treatment for severe acne, or acne non-responsive to other treatment options. Primarily due to its teratogenic effects, the use of isotretinoin has been strictly regulated and supervised in women of childbearing age, but many other side effects have been well documented. As early as in 1983, the first reports on excess granulation tissue resembling pyogenic granuloma within resolving acne lesions and around nails, were published in patients treated with oral isotretinoin for acne and with etretinate for psoriasis, respectively (1, 2). Although these side effects are probably not so rare, there are very few reports published in the world literature describing their clinical course and treatment modalities.

Here we report on two men treated with oral isotretinoin for severe acne who developed paronychia and periungual pyogenic granuloma-like lesions.

Case reports

Case 1

An otherwise healthy 18-year-old male received isotretinoin therapy for severe facial acne at a dosage of 60 mg per day (0.7 mg/kg). After two months of therapy, he noticed lesions on his fingers. On examination, he presented with painful erythema and slight edema on the periungual skin on several fingers with painful and eroded excessive granulation tissue over the nail folds on the left third, and right fourth finger (Figures 1 and 2). Antiseptic lotions

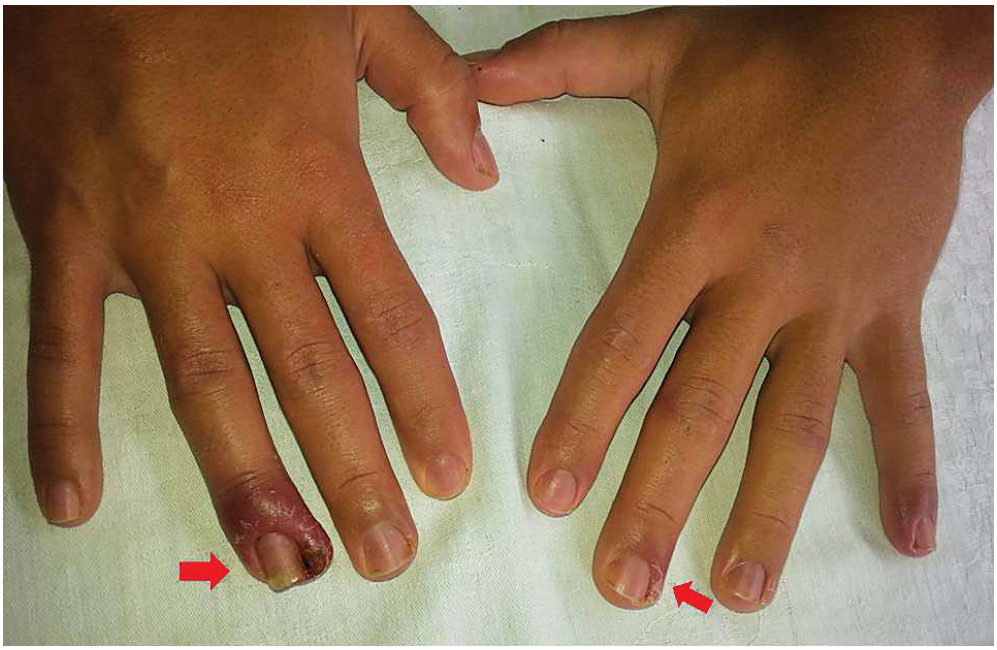

Figure 1. Excess periungual granulation tissue and paronychia on figers of both hands (arrows).

and antibiotic ointment were ineffective. He stopped taking isotretinoin, and all lesions disappeared within 3 weeks.

Case 2.
A 19-year-old male with severe nodular acne on the face and upper back received isotretinoin at a dose of 80 mg daily (0.9 mg/kg). Six weeks after the beginning of treatment, he developed painful paronychia of all fingers with several pyogenic granuloma-like nodules on lateral nail folds. The isotretinoin dosage was reduced to 60 mg daily without benefit, so two weeks later he quit the drug, and all lesions regressed within 2 weeks.

Discussion

Inflammation of the periungual tissue progressing to painful and bleeding pyogenic granuloma-like lesions is a well-known side effect of some drugs, like oral and topical retinoids (3 - 7). Paronychia is an infection of the distal and lateral nail folds, with associated excess granulation tissue. Usually multiple fingers and/or toes, rarely all, are involved, and in some patients rechallenge with isotretinoin leads to a secondary flare-up, suggesting causality. A recent retrospective study of 1.743 patients treated with oral isotretinoin, showed »periungual granuloma« in 2.1% of subjects (8). Similar lesions may be observed particularly with newer targeted therapies (9 - 11), like epidermal growth factor receptor (EGFR) inhibitors (9, 12) and mitogen-activated protein kinase kinases (MEKs) (13).

A number of new cancer drugs have recently been approved. Contrary to conventional chemotherapy, EGFR inhibitors have low hematotoxicity. Their side effects profile is distinct from older antitumor drugs, especially with regard to the skin. Regarding classification of their adverse cutaneous effects, EGFR inhibitors associated painful periungual inflammation (paronychia), that often arises from the nail wall and is associated with abundant formation of granulation tissue, has been classified in the third major group of cutaneous toxicity (9). Cutaneous toxicity may be interpreted as a stress response that affects epidermal homeostasis. Stress signals are transmitted to effectors in the cells which may produce an inflammatory response (9). MEK inhibitors inhibit the same signaling pathways as the EGFR inhibitors. It is well known that kinases play an important role in many intracellular signaling pathways, including those that control cell growth and cell division, such as mitogen-activated protein kinases (MAPKs). The kinases that phosphorylate and activate MAPKs, are known as MAP kinase kinases (MEKs).

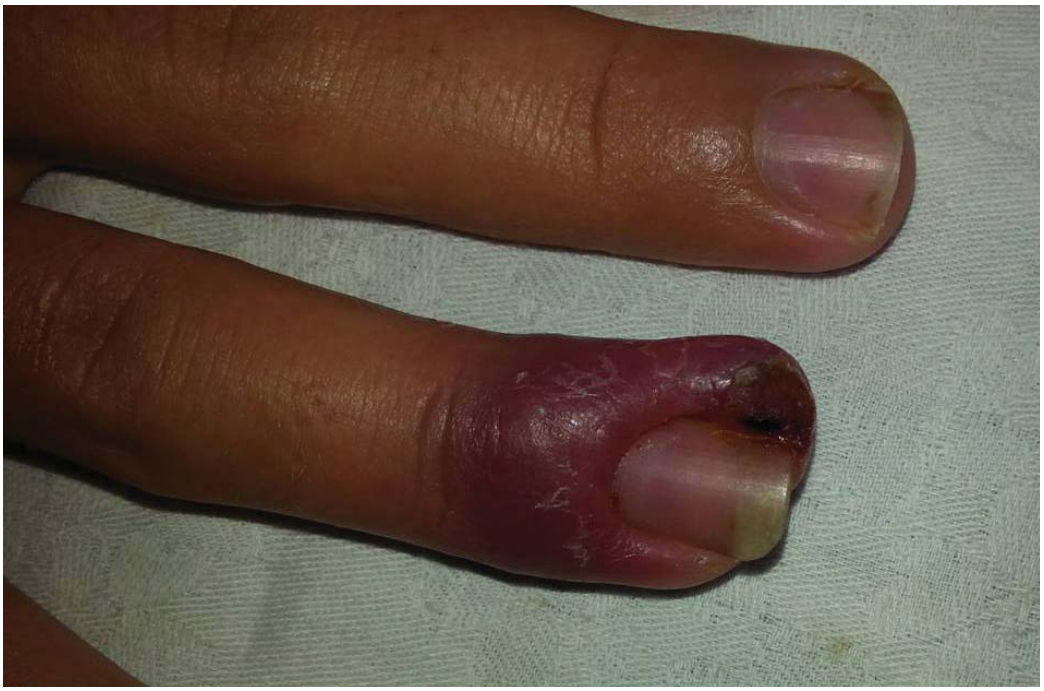

Figure 2. The lesion on the right fourth digit showing massively swollen periungual tissue, erythema, and erosion with maceration

Because EGFR signals downstream also through MEK signaling pathway, it can be expected that MEK inhibitors therefore cause similar cutaneous adverse events as EGFR inhibitors. Indeed, there was clinically a biphasic cutaneous side effect profile as was also reported for EGFR inhibition (13). A papulopustular rash in the seborrhoeic area was observed in acute phase, while xerosis cutis, fissured finger tips or paronychia with abundant formation of granulation tissue developed in the late phase. The histology of these lesions revealed that MEK inhibition mainly targeted the basal keratinocytes, since they are normally characterized by high EGFR expression; the reduced basal cell proliferation was compensated by increased suprabasal proliferation produced by self-amplifying cells within the suprabasal layer (13).

The lesions in acne patients treated with isotretinoin have not been biopsied, so we have to infer about their histopathologic features from similar lesions induced by other drugs which were sampled, e.g. inhibitor of EGFR (gefitinib). The lesions showed marked inflammation and numerous and prominent vessels in the dermis infiltrated with inflammatory cells consisting mostly of plasma cells, lymphocytes, and some neutrophils (12).

We can only speculate about the pathogenesis of retinoid-induced periungual excessive granulation tissue. Retinoids are known to promote wound healing in the early stages, accumulation of mononuclear cells in the dermis, and stimulate collagen synthesis. These factors may increase the patient's susceptibility to overgrowth of new granulation tissue (2). Isotretinoin affects expression of many genes, such as those known to encode extracellular matrix proteins which are therefore consistently upregulated (14). Although an increase in extracellular matrix may be consistent with the appearance of outgrowths, animal model studies have shown that 13-*cis* retinoic acid actually inhibits angiogenesis through inhibition of endothelial cell migration, tube formation, and altered cytokine production during the onset of angiogenesis (15). However, in other biologic systems, as in spermatogenesis, it was shown that signaling pathways induced by retinoic acid and MEK pathway are mutually exclusive (16), indicating that isotretinoin and MEK inhibitors may cause similar side effects.

Multiple therapeutic options of cutaneous side effects have been used, but few showed any consistent benefits (1-7). A two-week course of a potent topical

corticosteroid under occlusion and topical antibiotics have been suggested as first-line treatments for periungual pyogenic granulomas (4). Nevertheless, drug-induced pyogenic granuloma-like lesions resolved after withdrawal of the causal agent and reappeared on rechallenge (9, 13). Thus, in our case, withdrawal of isotretinoin was followed by complete and rapid resolution in both patients.

Conclusion

In conclusion, paronychia and excessive granulation tissue in the nail folds are not uncommon side effects of oral retinoids. It is therefore particularly important for practicing dermatologists to be aware that the best management approach is drug discontinuation.

Abbreviations

EGFR - growth factor receptor
MEKs - mitogen-activated protein kinase kinases
MAP2Ks - mitogen-activated protein kinases

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Periungvalni izraštaji slični piogenom granulomu tokom lečenja akni izotretinoinom – prikaz dva slučaja i pregled literature

Sažetak

Uvod. Periungvalni izraštaji slični piogenom granulomu nisu tako redak neželjeni efekat tokom lečenja izotretinoinom ali su do sada veoma retko opisivani u literaturi. U pitanju je najverovatnije idiosinkrazijska reakcija kod koje izotretinoin „priprema“ kožu pošto značajno utiče na sintezu komponenti vanćelijskog matriksa i rast novih krvnih sudova. Prvi slučajevi ekstenzivnog periungvalnog rasta granulacionog tkiva nalik na piogeni granulom tokom terapije retinoidima, koji su objavljeni u svetskoj literaturi 1983. godine, odnosili su se na izotretinoin tokom lečenja akni i etretinat u toku lečenja psorijaze.

Prikaz slučaja. U ovom radu prikazujemo dva naša

mlada pacijenta lečena oralnim izotretinoinom zbog teških akni, kod kojih je došlo do preteranog rasta periungvalnog granulacionog tkiva. Kod oba mladića su se promene spontano povukle posle prekida uzimanja leka.

Slučaj 1. Inače zdrav, 18 godina star mladić, lečen je zbog teškog oblika akni na licu izotretinoinom u dnevnoj dozi od 60 mg (0,7 mg/kgTT). Dva meseca posle započinjanja terapije, primetio je prve promene na prstima ruku (slike 1 i 2). Antiseptički losioni i antibiotske masti aplikovani su lokalno, ali nije bilo poboljšanja. Do potpune regresije svih promena došlo je u toku tri sledeće nedelje, pošto je izotretinoin u potpunosti obustavljen. Slučaj 2. Mladić star 19 godina sa teškim oblikom nodularnih akni na licu i leđima, inače zdrav, lečen je izotretinoinom u dnevnoj dozi od 80 mg (0,9 mg/kgTT). Šest nedelja nakon započinjanja lečenja, na svim prstima ruku, došlo je do pojave bolne paronihije a na lateralnim nokatnim naborima na pojedinim prstima razvili su se nodulusi slični piogenom granulomu. Doza izotretinoina je smanjena na 60 mg dnevno bez vidljivog efekta. Do potpune regresije svih promena došlo je u toku dve sledeće nedelje, pošto je izotretinoin u potpunosti obustavljen.

Diskusija. Inflamacija periungvalnog tkiva sa progresijom u bolne, krvavljenju sklone lezije nalik na piogeni granulom, dobro je poznati neželjeni efekat tokom primene pojedinih lekova, npr. sistemskih i lokalnih retinoida. U paronihiji dolazi do bujanja lateralnih i distalnih nokatnih nabora sa ekstremnim stvaranjem granulacionog tkiva. Obično je oboljenjem zahvaćen veći broj prstiju na nogama i na rukama, ređe svi. U onim slučajevima u kojima je pacijentima ponovo u terapiju uvođen izotretinoin, došlo je do sekundarnog recidiva, što ukazuje na kauzalnu vezu. Rezultati retrospektivne studije, koja je sprovedena na 1 743 pacijenta, pokazali su da je periungualni granulom imalo 2,1% svih izotretinoinom lečenih osoba. Identične promene mogu biti neželjeni efekti nove ciljane biološke terapije, npr. u toku primene inhibitora EGFR (eng. *epidermal growth factor receptor*) i inhibitora onih kinaza koje aktivišu mitogen-aktivisane kinaze – MEKs (eng. *mitogen activated kinase kinases*).

Veliki broj novih lekova sa antitumorskim ciljanim delovanjem nedavno je odobren. Za razliku od konvencionalne hemoterapije, lečenje ciljanim antitumorskim lekovima nove generacije povezano je sa manjim stepenom hematotoksičnosti. Neželjeni efekti terapije ovim lekovima se razlikuju od spektra klasičnih antitumorskih agenasa, naročito kada je profil neželjenih kutanih efekata u pitanju. Neželjeni kutani efekti su kategorisani u zavisnosti od težine i vremena njihovog javljanja u tri kategorije kutane toksičnosti. Neželjeni efekati u toku terapije inhibitorima EGFR, koje čine bolne paronihije sa ekscesivnim bujanjem granulacionog tkiva, ulaze u treću grupu kutane toksičnosti. Kutana toksičnost se može identifikovati sa odgovorom na stres koji narušava epidermalnu homeostazu. Stresni signali se u ćeliji prenose na efektore koji potom produkuju inflamatorni odgovor. Jedan isti signal može biti inhibisan i sa EGFR inhibitorima i sa MEK inhibitorima. Poznat je značaj koji kinaze, npr. MAPKs (eng. *mitogen activated kinases*), imaju u sistemima koji kontrolišu mnoge ključne intraćelijske procese kao što je kontrola rasta i deoba ćelije; MAPKs bivaju aktivisane fosforilacijom od strane MEKs. S obzirom da EGFR signali prolaze i kroz MEK signalne puteve, može se očekivati da njihovi inhibitori ispoljavaju ista neželjena dejstva na kožu. Rezultati ispitivanja koja su usledila potvrdili su ovu pretpostavku; u toku terapije MEK inhibitorima javio se bifazni kutani neželjeni profil koji se na isti način javio u toku terapije EGFR inhibitorima. U akutnoj fazi papulopustulozni osip izražen naročito u seboroičnim regijama, a kseroza kože, fisure na jagodicama prstiju ili paronihija s ekcesivnim bujanjem periungvalnog granulacionog tkiva u hroničnoj fazi (posle 6 nedelja).

O patogenezi bujanja ekscezivnog granulacijskog tkiva u toku terapijske primene retinoida, možemo samo spekulisati na osnovu njihovih dobro poznatih osobina na osnovu kojih mogu povećati prijemčivost za ekscesivno bujanje granulacionog tkiva: promovišu proces zarastanja rana u početnoj fazi; dovode do akumulacije mononuklearnih ćelija u dermis; stimulišu produkciju kolagena. Izotretinoin utiče na ekspresiju mnogih gena, npr. gena koji kodiraju sintezu ekstraćelijskih matriksnih proteina. Dok povećanje sinteze ekstraćelijskih matriksnih proteina može objasniti ulogu retinoida u bujanju granulacijskog tkiva, u eksperimentima na životinjama, utvrđeno je da 13-*cis* retinoična kiselina inhibiše angiogenezu putem inhibicije migracije endotelnih ćelija,

formiranja cevi i produkcije citokina. Bez obzira na ove kontroverze, u drugim biološkim sistemima, npr. spermatogenezi, pokazano je su mehanizmi delovanja retinoida i MEKs isključivi, što ukazuje na mogućnost da izotretinoin i MEKs inhibitori mogu proizvesti iste neželjene kutane efekte.

Mnogi terapijski modaliteti isprobani su sa ciljem kupiranja navedenih neželjenih kutanih efekata, ali bez željenog efekta. Potpuno ukidanje inkriminisanog leka, u našem slučaju izotretinoina dovodi do potpune sanacije lezija, a u slučajevima u kojima je izotretinoin ponovo uvođen u terapiju, dolazilo je do ponovnog recidiva periungvalnih lezija, što ukazuje na njihovu uzročno-posledičnu povazanost.

Zaključak. Prikazom dva slučaja periungvalnih izraštaja sličnih piogenom granulomu ističemo da svaki dermatolog treba da zna da oni nisu tako redak neželjeni efekat tokom lečenja izotretinoinom; jedino prestanak uzimanja leka može dovesti do njihove sanacije i to u kratkom vremenskom periodu.

Ključne reči

Piogeni granulom; Bolesti noktiju; Izotretinoin + neželjena dejstva; Acne vulgaris; Prikazi slučajeva; Pregled literature

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Clinical, Histological and Dermoscopic Findings in Familial Cylindromatosis: a Report of Two Cases

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Abstract

Cylindromas are benign appendage tumors mainly found on the scalp, but they can occur on any hair-bearing skin. Mutations in the cylindromatosis (CYLD) gene, a tumor suppressor gene located on chromosome 16q12–13, are responsible for multiple cylindromas, which are usually inherited in an autosomal dominant way, as in familial cylindromatosis and Brooke-Spiegler syndrome. The latter is characterized by the presence of multiple cylindromas, multiple trichoepitheliomas and spiradenomas. Based on genetic studies and the identification of heterozygous mutations in the same CYLD gene in familial cylindromatosis, multiple familial trichoepitheliomas, and the Brooke–Spiegler syndrome, it is suggested that these three conditions have the same genetic basis and are phenotypic expressions of the same disease. The diagnosis of each of the tree conditions is based on the dominant tumor type: cylindroma in familiar cyindromas, trichoepithelioma in multiple familial trichoepitheliomas, or a variety of skin appendage tumors including cylindromas, spiradenomas and trichoepitheliomas in Brooke-Spiegler syndrome. The onset of the disease is usually in the early adulthood, but may also occur in childhood or adolescence.

We report on two sisters, 37 and 43 years of age, with multiple cylindromas on the face and the scalp. Both patients reported that their mother also had multiple tumors on her head. Dermoscopy revealed arborizing vessels on a white-ivory or pink background, resembling dermoscopic features of basal cell carcinoma, though histopathological analysis revealed cylindroma.

In conclusion, in this study we report two cases of a very rare familial cylindromatosis, presenting with multiple benign cylidromas with dermoscopic features of basal cell carcinoma. All patients with multiple cylindromas in familial cylindromatosis should be counseled about increased risk for developing further tumors. Systemic and multidisciplinary approach with follow up is strongly recommended.

Key words

Neoplasms, Multiple Primary; Dermoscopy; Skin Neoplasms; Scalp; Neoplastic Syndromes, Hereditary; Case Reports; Mutation; Histological Techniques

Familial cylindromatosis is a rare hereditary disorder characterized by the presence of multiple cylindromas predominantly located on the scalp, face and neck (1). The onset of the disease is usually in the early adulthood, but may also occur in childhood or adolescence. Clinically, cylindromas are benign, rare, skin appendage tumors mainly found on the scalp, but they can occur on any hair-bearing skin. The lesions classically present as painless, smooth pink nodules, which may be either solitary or clustered together. They are slow-growing and different in size, which ranges from a few millimeters to over six centimeters. Mutations in the cylindromatosis (CYLD) gene, a tumor suppressor gene located on chromosome 16q12–13, are responsible for multiple cylindromas, which are usually inherited in autosomal dominant fashion, as in familial cylindromatosis and Brooke-Spiegler syndrome (BSS) (1, 2, 3). The latter, also inherited

by autosomal dominant transmission, represents a rare hereditary disorder characterized by the presence of multiple cylindromas, multiple trichoepitheliomas and spiradenomas. Based on genetic studies and the identification of more than heterozygous mutations in the same CYLD gene in familial cylindromatosis, multiple familial trichoepitheliomas and the Brooke–Spiegler syndrome, it is suggested that these three conditions have the same genetic basis and are phenotypic expressions of the same disease, now viewed as allelic variants with overlapping phenotypes (2, 4, 5).

The diagnosis of each of the three conditions is based on the dominant tumor type: cylindroma in familiar cyindromatosis, trichoepithelioma in multiple familial trichoepitheliomas, or a variety of skin appendage tumors including cylindromas, spiradenomas and trichoepitheliomas in BSS. From the aspect of clinical features, in terms of prognostic information for patients, this classification is not valuable, and therefore the term CYLD cutaneous

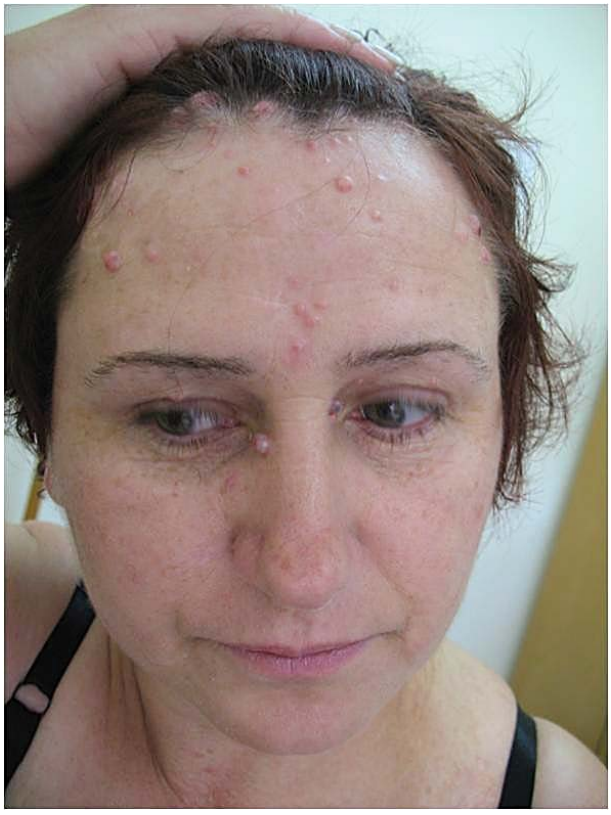

Figure 1. Multiple pinkish nodular lesions on the scalp and face

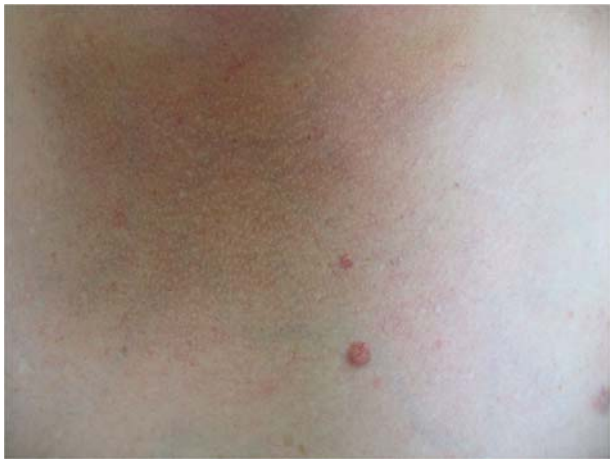

Figure 2. Nodular reddish lesions on the trunk

syndrome has been proposed (6). Up to now, more than 68 different mutations of CYLD gen have been identified (7, 8). The loss of this gene causes activation of NF-B which is a transcription factor with antiapoptotic activity (9).

Generally, benign multiple cylindromas may occasionally become malignant, particularly if present within BSS (10). In this study, we report on two cases of a very rare familial cylindromatosis in two sisters with multiple benign cylidromas with dermoscopic features of basal cell carcinoma.

Case reports

Case 1

A 43-year-old woman was referred to our Clinic with multiple painless nodular lesions, mainly distributed

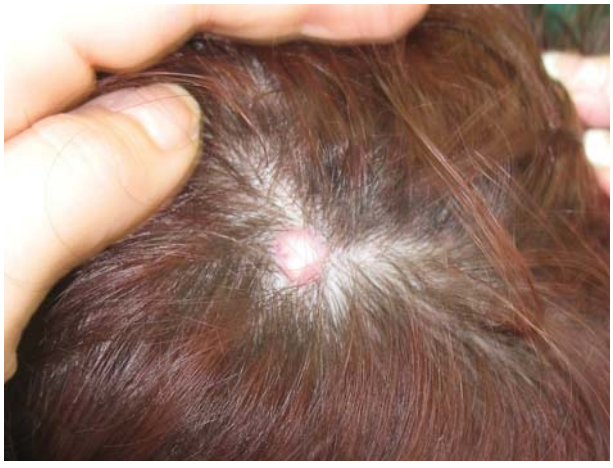

Figure 3. Nonpigmented nodular lesion on the scalp

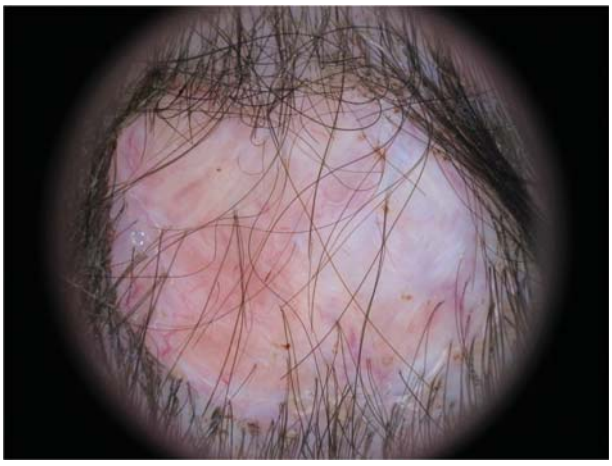

Figure 4. Dermoscopy of a nodular lesion on the scalp revealed pinkish coloration and a discrete vascular pattern

on the scalp and face, although sporadic lesions were also noticed on the trunk. The first lesion appeared at the age of 38 on the scalp, and their number increased over the following years. Clinically, all lesions were dome shaped, reddish nodules of different size (from 3 mm to 3 cm) located mainly on the head and scalp and sporadically on the trunk (Figures 1 and 2). Dermoscopy showed absence of pigmented network and presence of white-ivory background with visible discrete polymorphous vessels (Figures 3 and 4). Several lesions were excised and histopathological analysis showed non-encapsulated nodules arising from the dermis, forming multiple irregular well defned cell islands, arranged in a jigsaw puzzle-like pattern, surrounded by an eosinophilic hyaline sheath, a pattern corresponding to diagnosis of cylindroma (Figure 5).

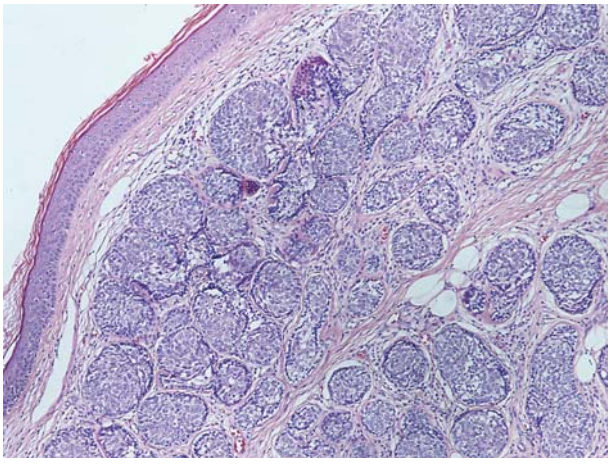

Figure 5. Non-encapsulated tumor arising from the dermis, forming irregular tumor islands, distributed in an aptly named "jigsaw" pattern. Surrounding the tumor islands, in discrete droplets within the nodules is a thick hyaline deposit

Due to possible association with other diseases, among other relevant analyses, ultrasound and computed tomography (CT) of parotid glands were performed, without any abnormalities detected.

Case 2

A 37-year-old woman, the sister of case 1, presented with multiple nonpigmented nodular lesions on the head and neck (Figures 6, 7). The tumors were neither pruritic nor tender. Dermoscopy of lesions revealed arborizing vessels on a white-ivory or pinkish background, mimicking basal cell carcinoma (Figure 8). The arborizing vessels were more prominent at the periphery of lesions, while in some tumors blue dots and globules were also detected (Figure 9). Histopathological analysis of excised tumors corresponded to cylidromas (Figure 10). Ultrasound of parotid glands and CT were also performed with no abnormalities detected.

Both patients reported that their mother also had multiple tumors on her head.

After clinical evaluation of both cases, some lesions were recommended to be excised for esthetic reasons, due to rapid growth, or compression. Further follow-up was recommended.

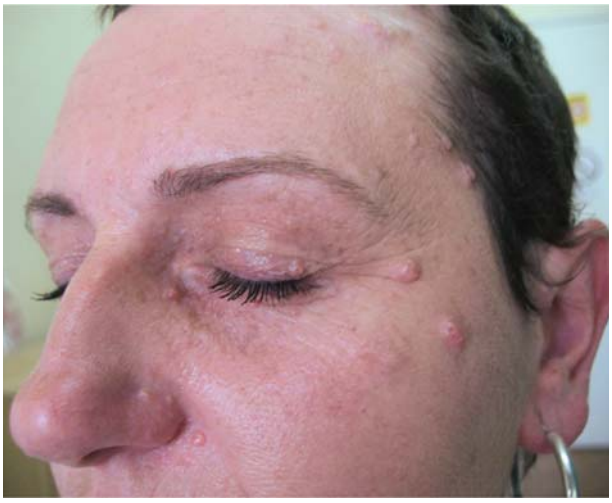

Figure 6. Multiple nonpigmented lesions on the face

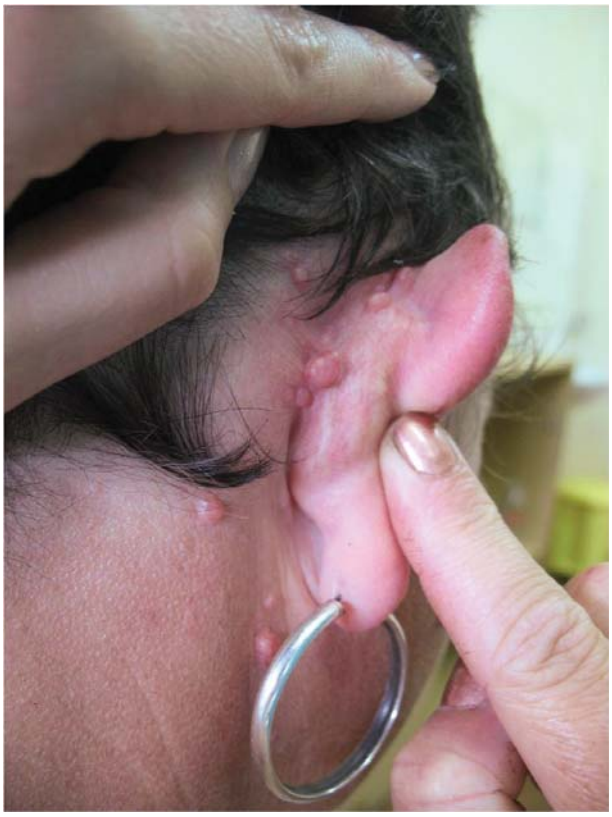

Figure 7. Pinkish lesions in the retroauricular region

Discussion

Though being classified upon morphological similarity to normal appendage structures, clinical appearance of adnexal tumors is usually non-specific. They are not diagnosed as such until after histopathological analysis. However, if the tumor shows ductal differentiation,

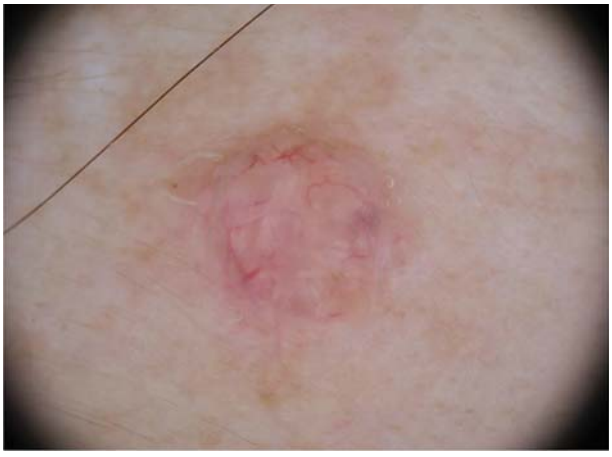

Figure 8. Dermoscopy revealed arborizing vessels at the periphery of the lesion

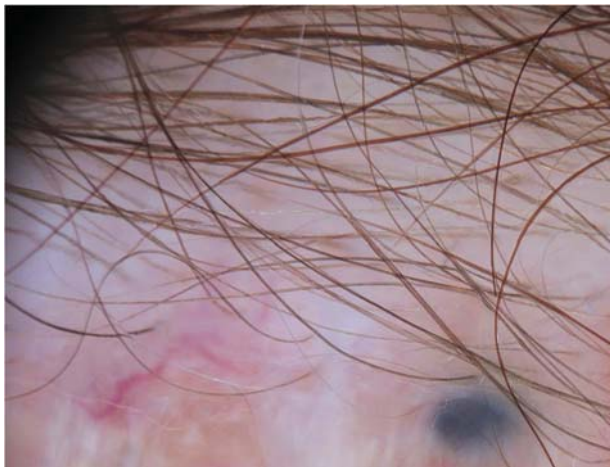

Figure 9. Blue globule on the whitish-pink background was detected by dermoscopy

it may be either eccrine or apocrine. Because there are no histochemical or immunohistochemical stains that allow distinction between eccrine and apocrine tumors, their differentitation is not possible, unless there is concomitant follicular appearance present. Therefore, tumors traditionally considered to be of eccrine differentiation, such as cylindroma, may show either line of differentiation, and this is probably most often apocrine (1). The aforementioned coexistence of multiple cylindromas with follicular tumors such as trichoepitheliomas, confirms apocrine line of differentiation at least in a certain number of these tumors. In some patients, there may be an admixture

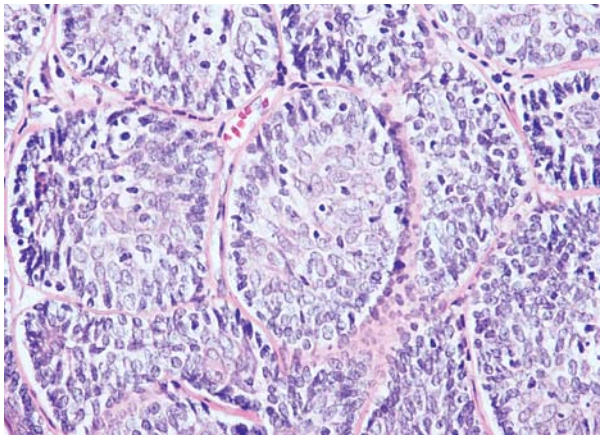

Figure 10. Two populations of cells are noted to make up the tumor nodules. A smaller cell with a hyperchromatic nucleus tending to the periphery, and larger cells with open nuclei throughout the centre of the nodule

with trichoepithelioma, either in separate tumors or sometimes in the same tumor (1). Moreover, multiple trichoepitheliomas develop from undifferentiated germinative cells of the pilosebaceous – apocrine unit (11), which explains why in some cases they have features of spiradenoma and/or cylindroma, particularly in BSS (1).

Two sisters in our study were diagnosed based on tree conditions of the dominant tumor type, e.g. being cylindroma in familiar cyindromatosis (5). Clinical examination of all skin tumors showed that both sisters had similar tumor features, which corresponded to one tumor type, naimely cylidroma. The tumors were painless, different in size, with uniform dome shaped reddish appearance and typical localization. In both sisters dermoscopic examination of cylidromas revealed whitish-pinkish background with discrete vascular pattern, and some arborizing telangiectasia. Although, arborizing vessels are dermoscopic features of basal cell carcinoma, this dermoscopic feature is also seen in cylidromas. Unlike in basal cell carcinomas, where arborizing vessels are more pronounced in the center, in case of cylindromas, vascular branches are more pronounced at the periphery. This observation may help in differentiation of basal cell carcinoma and cylindroma. There are currently only a few case reports on the dermoscopic features of cylindromas in the medical literature. The reported dermoscopic patterns of cylindromas include arborizing vessels on whitish-pinkish background, blue dots and globules, like in our cases. Without doubt, more studies are needed to establish the definite dermoscopic patterns of cylindromas.

Spiradenomas are often seen in conjunction with cylindromas in BSS, but they are rather painful, typically presenting with dermal nodules and blue/black appearance (2). Definitive diagnosis of cylindroma and spiradenoma requires histopathological analysis (5). Histopathologically, cylindromas exhibit a typical appearance composed of nests of basaloid cells arranged into mosaic-like masses (jigsaw-puzzle) in cross section resembling a cylinder (1).

This histopathological finding should raise the suspicion of a germline CYLD gen mutation in a young individual. In those with a mutation in CYLD gen, the penetrance in terms of tumor development is almost 100%. Individuals with a family history, but without tumors, are at 50% risk of having a CYLD mutation. Genetic testing (unfortunately not available for us), allows individuals to assess their own risk as well as family planning. Testing can be performed using PCR for patients with: 1. multiple cylindromas, spiradenomas or trichoepitheliomas; 2. a single cylindroma, spiradenoma or trichoepithelioma and an affected first-degree relative with any of these tumors; 3. an asymptomatic family member at 50% risk with a known mutation in the family (5). More recently, the presence of dysregulated tropomyosin kinase (TRK) signalling, in patients with germline CYLD mutations, was detected and the treatment effficacy of lestaurtinib, a TRK inhibitor, was established in vitro (12). The morbidity associated with skin appendage tumors can be very high because the tumors are disfiguring, even causing sexual dysfunction. Different treatment choices available for adnexal tumors in BSS patients include excision of the tumor, dermabrasion, electrodesiccation, cryotherapy and radiotherapy using argon and C02 laser. There are proofs that aspirin and its derivatives can result in new adnexal lesions in these patients (13).

Although malignant transformation is very rare, there are reports of malignant transformation of dermal cylindromas and possibility of metastases to the lymph nodes, thyroid, liver, lungs and bones, causing hemorrhage and even meningitis (10). So far, less than 50 cases of cylindrocarcinomas have been reported in literature (14, 10). However, patients with BSS are not only prone for malignant transformation of their cylindromas, but also for developing benign or malignant tumors in tissues other than skin appendages, particularly of the salivary glands (15).

Conclusion

In this study we report two cases of a very rare familial cylindromatosis presenting as multiple benign cylidromas with dermoscopic features of basal cell carcinoma. All patients with multiple cylindromas in familial cylindromatosis should be counseled about increased risk for developing further tumors. Systemic and multidisciplinary approach with further follow up is always recommended.

Abbreviations

CYLD - cylindromatosis gene
NF-B - nuclear factor-B
BSS - Brooke-Spiegler syndrome

CT - computed tomography
PCR - polymerase chain reaction
TRK - tropomyosin kinase
CO_2 - carbon dioxide

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Kliničke, histološke i dermoskopske karakteristike familijarne cilindromatoze – prikaz dva slučaja

Sažetak

Uvod. Cilindromi predstavljaju benigne tumore adneksa kože, koji se lokalizuju pretežno na glavi ali mogu zahvatiti bilo koju drugu regiju kože sa folikulima dlake. Mutacije koje se javljaju u tumor-supresorskom genu na hromozomu 16q12–13, koji je nazvan cilindromatoza-CYLD gen, odgovorne su za njihov nastanak. Kada su prisutni u većem broju, npr. u familijarnoj cilindromatozi i Bruk–Špiglerovom (Brooke-Spiegler) sindromu, cilindromi se autozomno dominantno nasleđuju. Pored multiplih cilindroma i multiplih spiradenoma, u Bruk–Špiglerovom sindromu prisutni su i multipli spiradenomi.

Na osnovu rezultata genetskih ispitivanja i identifikacije u familijarnoj cilindromatozi, Bruk–Špiglerovom sindromu i u multiplom familijarnom trihoepiteliomu, heterozigotnih mutacija u istom CYLD genu, pretpostavlja se da ova tri različita oboljenja imaju istu genetsku osnovu te da se radi o tri fenotipske ekspresije jednog istog poremećaja. Dijagnoza se postavlja na osnovu prisustva dominantnog tumora, u familijarnoj cilindromatozi to je cilindrom, u multiplom familijarnom trihoepiteliomu je trihoepitelioma, dok je u Bruk–Špiglerovom sindromu prisutno nekoliko različitih adneksalnih tumora kože, uključujući cilindrome, spiradenome i trihoepiteliome. Pojava tumora je najčešća u ranom adultnom periodu života ali se mogu javiti i u detinjstvu i kasnije, uglavnom do četvrete decenije života.

Prikaz slučaja. U radu su prikazana dva slučaja familijarne pojave multiplih cilindroma na licu i

poglavini kod dve rođene sestre, četrdesetogodišnje i tridesetsedmogodišnje ženske osobe, koje su u anamnezi obe navele da i njihova majka ima tumore po glavi. Klinički su sve lezije, kod obe sestre, imale uniformni izgled u formi ružičastih do crvenkastih jasno definisanih tumorskih formacija u vidu nodusa različite veličine, dijametra od 3 mm do 3 cm, lokalizovanih na licu vratu i glavi i sporadično na trupu (slike 1, 2, 3, 6 i 7). Lezije nisu izazivale osećaj ni bola niti svraba. Dermoskopskom analizom lezija u oba slučaja, uočeni su arborizovani krvni sudovi na beloj, boje slonovače ili ružičastoj osnovi (slike 4 i 8). Arborizovani krvni sudovi su bili uočljiviji na periferiji, u nekim tumorima detektovane su plave tačke i globule (Slika 9), nalaz koji se može videti i u bazocelularnom karcinomu. Histopatološkom analizom utvrđeno je prisustvo neinkapsulisanih nodusnih formacija dermalnog ishodišta, formiranih od većeg broja nepravilnih ćelijskih ostrvaca, jasno ograničenih i međusobno razdvojenih eozinofilnim hijalinskim depozitom u vidu membrane – nalaz koji je odgovarao histološkim osobinama cilindroma (slike 5, 10).

Diskusija. Dijagnoza je kod obe sestre postavljena na osnovu stava da se dijagnoza sva tri oboljenja zasniva na dominantnom tumoru, npr. to je cilindrom u familijarnoj cilindromatozi. Kod obe sestre, sve promene su imale klinički izgled koji je bio kompatibilan sa onim u cilindromu. Iako su arborizovani krvni sudovi u dermoskopskom nalazu karakteristika bazocelularnog karcinoma, mogu se videti i u drugim promenama, npr. cilindromu. Za razliku od bazocelularnog karcinoma kod koga su arborizovani krvni sudovi jače izraženi u centru lezija, u cilindromu vaskularni elementi su naglašeni periferno, što olakšava postavljanje diferencijalne dijagnoze. Dermoskopske osobine cilindroma nisu dovoljno dobro definisane zbog malog broja objavljenih radova. Pored arborizovanih krvnih sudova na bledoružičastoj osnovi, u dermoskopskom nalazu cilindroma opisane su i plave tačke i globule, takođe dermoskopske karakteristike bazocelularnog karcinoma.

Spiradenomi se često javljaju udruženo sa cilindromima kao što je to u Bruk–Špiglerovom sindromu, ali se od njih razlikuju klinički karakterističnom plavo-crvenom prebojenošću i bolni su. Za postavljanje definitivne dijagnoze cilindroma i spiradenoma neophodna je patohistološka analiza, s obzirom na tipični nalaz u cilindromu za koji su karakteristična gnezda bazaloidnih ćelija organizovana u vidu mozaika, koji na poprečnim presecima podsećaju na cilindre.

Patohistološki nalaz koji ukazuje na cilindrom treba kod mlade osobe da pobudi sumnju na prisustvo mutacije u CYLD genu. Kod osoba koje poseduju mutaciju na CYLD genu, penetracija u smislu pojave tumora je skoro 100%. Kod osoba koje imaju obolele srodnike, a sami nemaju promene, rizik da imaju CYLD mutacije iznosi 50%. Genetsko testiranje (nama nažalost nije bilo dostupno), omogućuje određivanje postojanja rizika i planiranje porodice. Teba ga sprovoditi pomoću PCR tehnike u slučaju postojanja: 1. multiplih cilndroma, spiradenoma ili trihoepitelioma; 2. pojedinačnog cilindroma, spiradenoma ili trihoepitelioma i obolelog srodnika prvog reda sa bilo kojim od navedenih tumora; 3. člana porodice bez simptoma sa 50% rizikom i postojanjem mutacije u porodici. Nedavno je kod osoba koje imaju mutaciju na CYLD genu utvrđena disregulacija tropomiozin kinaznog signalnog puta, posle čega je usledilo ispitivanje čiji rezulatati su potvrdili terapijsku efikasnost flestauriniba inhibitora tropomiozin kinaze in vitro.

Stopa morbiditeta kod osoba sa adneksalinim tumorima je visoka s obzirom na estetski aspekt koji u pojedinim slučajevima može izazvati seksualnu disfunkciju i ozbiljno narušiti kvalitet života obolelog! Terapija podrazumeva brojne modalitete: totalna hirurška ekscizija, dermoabrazija, elektrodisekacija, krioterapija, argonski i CO2 laser. Postoje dokazi da aspirin i njegovi derivati izazivaju pojavu novih promena a pokušaji lečenja lokalnom primenom salicilne kiseline nisu dali zadovoljavajuće rezultate.

Iako je maligna transformacija veoma retka, postoje objavljeni slučajevi metastaziranja maligno transformisanog dermalnog cilindroma u limfne čvorove, štitastu žlezdu, jetru, pluća i kosti, sa pojavom meningitisa i krvarenja. Do sada je u svetskoj literaturi objavljeno oko 50 slučajeva cilindrokarcinoma. Osobe sa Bruk–Špiglerovim sindromom ne samo da poseduju veći rizik za malignu alteraciju cilindroma, nego i za pojavu benignih ili malignih tumora u drugim tkivima, naročito u pljuvačnim žlezdama.

Zaključak. U ovom radu je prikazan veoma redak slučaj familijarne cilindromatoze sa multiplim benignim cilindromima koji su imali dermoskopske

karakteristike bazocelularnog karcinoma. Svim osobama koje imaju familijarnu cilindromatozu treba predočiti da imaju povišeni rizik za nastanak novih tumora. Sistemski i multidisciplinarni pristup uz redovno praćenje obolelog predstavlja osnovni postulat.

Ključne reči

Multiple primarne neoplazme; Dermoskopija; Tumori kože; Skalp; Hereditarni neoplastični sindromi; Prikazi slučajeva; Mutacija; Histološke tehnike

A Report on the 4th World Congress of Dermoscopy and Skin Imaging

The 4th World Congress of Dermoscopy and Skin Imaging was held from 16th- 18th April, 2015 in Austria's capital, Vienna, at the magnificent Hofburg Palace. It was the largest dermoscopy event so far, with more than 1.300 participants from 66 countries. Besides numerous lectures by invited speakers, there were more than 300 other presentations, of which 66 were free communications, and 265 poster presentations. More than 30 industry companies presented various, mostly skin imaging devices and equipment.

The Congress started with the 3rd International Dermoscopy Society Consensus Conference, which resulted in a decision to publish a dictionary of approved dermoscopic terms and specific definitions. During the 3-days program, a wide spectrum of topics were covered: screening and prevention of skin cancers, monitoring of patients at risk, skin cancer surgery, dermatopathology, total body photography, teledermatology, confocal microscopy, optical coherence tomography, dermoscopic controversies,

Figure 1. Gathering at the poster session: poster presentations "Rainbow pattern in malignant skin lesions other than Kaposi sarcoma: case series report" and "Clinical and dermoscopic findings in Brooke–Spiegler Syndrome – a report of two cases", both by Željko Mijušković, Lidija Kandolf Sekulović, Danica Tiodorović Živković and Tatjana Roš

Figure 2. Dermatoscopy World Championship: the Serbian team against the Egyptian team

dermoscopy in inflammatory diseases etc, with many workshops offered.

Our delegation had two invited speakers: Danica Tiodorović Živković presented "Typical cases from Serbia" during the session "Dermatoscopy around the globe", and Danijela Dobrosavljević Vukojević spoke about "Ex vivo dermatoscopy for pathologists" during the session "Recent advances in dermoscopy and skin imaging". Poster presenting authors were: Željko Mijušković, Lidija Kandolf Sekulović, Danica

Figure 3. Enjoying dinner at Kursalon: Milana Ivkov Simić, Jadranka Krstić, Tatjana Roš, Dušan Škiljević, Ljiljana Medenica, Jelena Stojković Filipović and Željko Mijušković…

Figure 4. While others were having fun at the party at the Porgy and Bess Jazz Club: Lidija Kandolf Sekulović, Danica Tiodorović Živković and Elvira Moscarella

Tiodorović Živković, Jelena Stojković Filipović, Vesna Mikulić and Tatjana Roš.

An interesting novelty was Dermatoscopy World Championship, where contestants were expected to set a diagnosis on parts of jigsaw puzzle dermoscopic images. The Serbian team members: Tiodorović Živković – Mijušković - Roš, had beaten the French and Egyptian teams, but lost in the 3rd round to the world champions themselves, the Polish team.

The friday night was fun, with the famous *Los Globulos Marrones* band performing at the Porgy&Bess Jazz Club. Geppi Argenziano on drums, Harald Kittler, Daniele Striano, Patrizio Sepe and Luc Thomas on guitars, Peter Bourne and Philipp Tschandl on keys, really amused colleagues playing classics that night.

The 5th IDS World Congress will take place in Thessaloniki, Greece, in June 2018**.** Looking forward!

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2015/2016

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
8-11 July, 2015	4th World Psoriasis and Psoriatic Arthritis Conference, Stockholm, Sweden	5 March, 2015	www.ifpaworldconference.com
21-22 July, 2015	2nd International Workshop on Dermatology, Istanbul, Turkey	15 May, 2015	www.med-scoop.org/iwdr/
28 July -1 August, 2015	4th International Summer Academy of Practical Dermatology, Munich, Germany	No deadline information	www.isa2015.com
5-9 September, 2015	27th European Congress of Pathology, Belgrade, Serbia	8 April, 2015	www.esp-congress.org
17-20 September, 2015	2nd Regional Congress of Corrective Dermatology of the 21st Century, Ljubljana, Slovenia	No abstract submission	http://www.kongres-korektivna-dermatologija.com
24-26 September, 2015	29th European Conference on Sexually Transmitted Infections, Barcelona, Spain	No deadline information	www.iusti2015.com
27-29 September, 2015	8th World Congress on Itch, Nara, Japan	15 June, 2015	www.itchnara.jp
1-4 October, 2015	36th Annual Meeting of the International Society for Dermatologic Surgery, Seoul, Korea	31 July, 2015	www.isdsworld.com
7-11 October, 2015	24th EADV Congress, Copenhagen, Denmark	19 April, 2015	www.eadvcopenhagen2015.org
9-12 October, 2015	7th Trends in Medical Mycology, Lisbon, Portugal	1 June, 2015	www.timm2015.org
16 October, 2015	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
28-31 October, 2015	11th EADO Congress, Marseille, France	7 June, 2015	www.eado-melanomacenters-marseille2015.com
5-7 November, 2015	18th Belgrade Dermatology Days, Belgrade, Serbia	15 September, 2015	www.udvs.org
18-21 November, 2015	9th World Congress for Hair Research, Miami, Florida, USA	26 May, 2015	www.hair2015.org
5-8 May, 2016	13th EADV Spring Symposium, Athens, Greece	10 January, 2016	www.eadvathens2016.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 of literature 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 should be submitted to the **Editor in Chief: Prof. Dr. Marina Jovanović***, Clinic of Dermatovenereologic Diseases, Clinical Center of Vojvodina, Hajduk Veljkova 1-3, Novi Sad, Serbia, by mail to: serbjdermatol@open.telekom.rs.*

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 of the article, which should be 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 should 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 non-standard 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://www.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. Additional information

Accepted manuscripts are edited and returned to the corresponding author for approval. 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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Cover figure: Christ Healing Ten Lepers, Christ's Miracles, 14th century, The monastery Visoki Dečani, Serbia, Kosovo

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