

# SERBIAN JOURNAL OF Dermatology and Venereology

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## ORIGINAL ARTICLES

Sero-epidemiology and risk factors of syphilis

Management of treatment-resistant alopecia areata with Platelet Rich Plasma

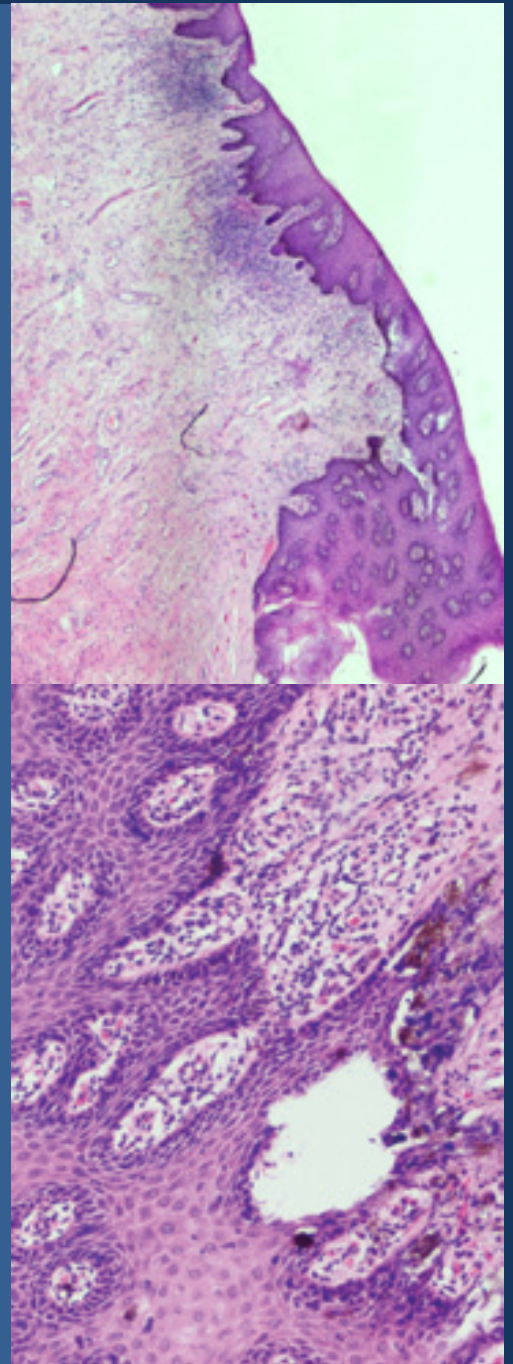
Bacterial Vaginosis in Pregnant Women at Maternal and Child Hospital

## CASE REPORTS

Unilateral mediothoracic exanthem in Indian children

DERMOSCOPY OF THE MONTH:  
Recurrent Vulvar Melanoma

## FORTHCOMING EVENTS





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# CONTENTS

Serbian Journal of Dermatology and Venereology 2019; 11 (2):41-74.

## ORIGINAL ARTICLES

- 43 Sero-epidemiology and risk factors of syphilis in Makassar, Indonesia**  
*Maryam KUSUMAWATY, Khairuddin DJAWAD, Muh NASRUM MASSI,  
Andi Muhammad ADAM, Siswanto WAHAB, Burhanuddin BAHAR*
- 50 Successful Management of Treatment-Resistant Alopecia Areata with Platelet Rich Plasma: A Case Series**  
*Sanjeevani FONSEKA , Y.M.D.M BANDARA, Brabaharan SUBHANI*
- 53 Bacterial Vaginosis in Pregnant Women at Maternal and Child Hospital, West Java, Indonesia, 2018: High Prevalence with Asymptomatic Symptoms**  
*Pati AJI ACHDIAT, Rasmia ROWAWI, Irma FAKHROSA, Hendra GUNAWAN,  
Reti HINDRITIANI, Oki SUWARSA, Reiva FARAH DWIYANA, Kartika RUCHIATAN,  
Agnes DWI HASTJARJARI*

## CASE REPORTS

- 61 Unilateral Mediosththoracic Exanthem: Case Reports of two Indian Female Children**  
*Shruti SHARMA, Rajesh L. PATHI, Anjali YADAV, Kamal AGGARWAL*

## DERMOSCOPY CASE OF THE MONTH

- 65 Recurrent Vulvar Melanoma - a Case Report**  
*Ljubica JEVREMOVIĆ JOVIČIĆ, Vesna KESIĆ, Miroslav L. ĐORĐEVIĆ, Miroslav DINIĆ,  
Nenad PETROV, Aleksandar SPASIĆ, Lidija KANDOLF SEKULOVIĆ*

## FORTHCOMING EVENTS

- 71 Dermatology and Venereology Events 2019**  
*Zorana KREMIĆ*



# Sero-epidemiology and risk factors of syphilis in Makassar, Indonesia

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## Abstract

**Introduction.** Syphilis is an infectious disease caused by *Treponema pallidum* spirochete and is mainly transmitted by sexual contact. Syphilis has the potential to cause serious complications and is closely related to human immunodeficiency virus (HIV) infection thus making syphilis still a major public health problem. In Indonesia, surveys of high-risk populations in 2007 and 2011 reported an increase in the prevalence of syphilis, especially in men who have sexual relationships with other men (MSM). Moreover, studies have described risk factors for HIV transmission including MSM, heterosexual contacts, Intravenous (IV) drug use, and infected partners. **Objectives.** To assess the epidemiological aspects and risk factors for syphilis in Makassar, as well as the correlation with a coinfection of other sexually transmitted infections. **Material and Methods.** This study is a multi-centre cross-sectional descriptive study with consecutive sampling. We evaluated cases for eligibility by confirming the diagnosis based on the serological result using rapid plasma reagin assay (RPR), *Treponema pallidum* haemagglutination (TPHA), and HIV screening kit. The cases were analyzed based on epidemiological features, risk factors and clinical findings, coinfection with other sexually transmitted infection (ST), and stadium of the disease. **Results.** A total of 79 serologically confirmed syphilis cases were collected between January 2017 and December 2018 in Makassar, the capital city of South Sulawesi province in Indonesia. Of the 63 male subjects (79.7%), 38 (48.1%) were homosexual/MSM, and in 41 cases of HIV-infected subjects, 25 (60.9%) of them were also MSM. **Conclusion.** Our study showed there was a significant correlation between syphilis and an increased risk of HIV transmission in MSM groups. The higher number of cases of syphilis and HIV co-infection among MSM can increase transmission of both infections and should be considered a major risk factor for syphilis in Makassar.

**Key words:** Syphilis Serodiagnosis; Risk Factors; Syphilis; Seroepidemiologic Studies; Sexually Transmitted Diseases; Homosexuality, Male; Indonesia

## Introduction

Syphilis is an infectious disease caused by *Treponema pallidum* spirochete and is mainly transmitted by sexual contact (1). Syphilis is divided into several stages, namely the primary, secondary and latent stage, in which clinical manifestations can develop from one stage to another if no appropriate treatment is given to the patient. Syphilis has the potential to cause serious complications and is closely related to HIV infection thus making syphilis still a major public health problem (2). Syphilis initially emerged in the 15th century, and its prevalence has declined by the 20th

century. However, over the last few decades, the prevalence increased again in American countries, Europe and Asia (3, 4). Studies in Australia reported an increase in the prevalence of syphilis, especially among MSM, although now syphilis is also increasing in the general population, especially among adolescents and young adults (5, 6). In Indonesia, surveys of high-risk populations were carried out by the Surveilans Terpadu Biologi Perilaku (STBP) in 2007 and 2011 and reported an increase in the prevalence of syphilis, especially in MSM with the prevalence of 4% to 13%. The highest prevalence of syphilis was

found in MSM populations, namely a total of 28% (7). Studies in the United States described that MSM (51%) was the most reported risk factor for HIV transmission, followed by high-risk heterosexual contacts (14%), IV drug user (9%), and MSM IV drug user (7%). They also stated that MSM living with HIV are 5 times more prone to syphilis co-infection, compared with heterosexual men with HIV (8). Serological tests are now the mainstay of workup diagnostics for syphilis (9). Antibody measurements are important for screening and diagnosis of syphilis. Two categories of antibodies are called "Non-treponemal" which are directed against phospholipid, and "treponemal" which is directed against the *Treponema pallidum* polypeptide used for this purpose. Non-treponemal antibodies are detected by the Rapid Plasma Reagin (RPR) test, the Venereal Disease Research Laboratory (VDRL) test, and the Tolidine Red Unheated Serum test (TRUST). Treponemal antibodies are detected by immunofluorescence in Fluorescent Treponemal Antibody Absorption tests (FTA-ABS) or by agglutination in *Treponema pallidum* Hemagglutination test (TPHA) or *Treponema pallidum* Particle Agglutination Assay (TP-PA) (10). In this study, the serological examination used was RPR and TPHA.

## Material and Methods

This study is a multi-centre cross-sectional descriptive study with consecutive sampling. Subjects were recruited from the outpatient

dermatovenereology clinic of Dr Wahidin Sudirohusodo Hospital and Hasanuddin University Dermatovenereology Department's networking hospitals in Makassar between January 2017 and December 2018. Makassar is the capital city of South Sulawesi province in Indonesia. Written consent was obtained from all participants in the study. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine Hasanuddin University (No. 470/H4.8.4.5.31/PP36-KOMETIK/2018).

We evaluated cases for eligibility by confirming the diagnosis of syphilis based on the serological result using qualitative and quantitative RPR and TPHA commercial kit (RPR AIM Cat. No. E RPR 2 and TPHA AIM Cat. No. TPHA E 100). All syphilis cases were also screened for HIV infection using widely available screening kit SD Bioline® HIV 1/2 3.0 (Standard Diagnostics, Suwon City, South Korea). The cases were analyzed based on epidemiological features (gender, age, marital status), risk factors and clinical findings (ulcer, fever, lymphadenopathy, skin rash, condylo-ma lata), co-infection with other STI (HIV, genital herpes, gonorrhoea, condylo-ma acuminata, candidiasis), and stadium of the disease. We were able to generate meaningful summary statistics and tabulated the results. Statistical analyses were performed using Statistical Package for Social Science 20 software (SPSS Inc., Chicago, IL, USA) then reported as mean and percentage.

**Table 1.** Demographic data of the patients

Variable	No.	%
Age, yrs, mean $\pm$ SD	30.19 $\pm$ 9.58	
Age Group		
11-20	10	12.7
21-30	41	51.8
31-40	15	19
41-50	9	11.4
>51	4	5.1
Gender		
Male	63	79.7
Female	16	20.3
Marital status		
Married	35	44.3
Non-married	44	55.7

## Results

A total of 79 serologically confirmed syphilis cases were collected, and the results showed that 79.7% were male and 20.3% were female (giving a male: female ratio of 4:1), whose age was between 17 and 57 years (mean  $\pm$  standard deviation (SD),  $30.19 \pm 9.58$  years) as shown in **Table 1**. The majority of subjects (51.8%) were from 21-30 age group and out of 55.7% who

were not married, 65.9% were homosexual. Demographic data of the patients are shown in **Table 1**.

## Risk Factors and Clinical Manifestations

Sexual intercourse was the major risk factor of contracting syphilis in the majority of patients including those of homosexual, bisex-

**Table 2.** Data on risk factors and clinical manifestations in the patients

Variable	No.	(%)
<b>Risk Factors</b>		
Homosexual/ MSM	38	
HIV-infected	41	
IV drug user	9	
Infected partner	5	
<b>History of Sexual Contact</b>		
Single partner	5	6.4
Multiple partners	43	54.5
Sexual worker	10	12.7
Unknown	21	26.4
<b>Sexual Orientation</b>		
Heterosexual	39	49.4
Homosexual/ MSM	38	48.1
Bisexual	2	2.5
<b>Clinical Manifestations</b>		
Ulcer	11	
Fever	12	
Lymphadenopathy	8	
Skin rash	20	
Palmoplantar rash	1	
Condyloma Lata	0	
<b>Co-infection with STIs</b>		
HIV	41	
Genital Herpes	4	
Gonorrhoea	10	
Condyloma Acuminata	27	
Candidiasis Vaginalis	16	
<b>Clinical Manifestations</b>		
Single	20	25.3
Multiple	9	11.4
Asymptomatic	50	63.3
<b>Stadium</b>		
Primary	10	12.6
Secondary	19	24.1
Latent	50	63.3

**Table 3.** Laboratory results of the patients

Variable	No.	%
<b>RPR</b>		
1:4	26	32.9
1:8	5	6.3
1:16	44	55.7
1:32	4	5.1
<b>TPHA</b>		
1:20	6	7.6
1:40	33	41.7
1:80	0	0
1:160	0	0
1:320	5	6.3
1:640	12	15.2
1:1280	19	24.1
1:2560	4	5.1
<b>HIV co-infection</b>		
Positive	41	51.9
Negative	38	48.1

ual and heterosexual orientation. Namely, of 63 male cases (79.7%) diagnosed with syphilis, 38 (48.1%) were homosexual/MSM, and of 41 cases of HIV-infected patients, 25 cases (60.9%) were homosexual/MSM. Heterosexual patients who were co-infected with HIV had a history of contact with sex workers. An increase in the number of syphilis cases in heterosexuals was related to the history of sex worker contact. Whereas out of 16 female patients, in 9 cases they were sex workers, 1 case of a sex worker with a history of IV drug user, 1 case of IV drug user and in 5 cases they contracted syphilis from the partner who was infected.

Clinical manifestations including fever, ulcer, lymphadenopathy, skin rash were also assessed and tabulated. A total of 11 patients came with ulcers accompanied by lymphadenopathy and 10 (12.6%) among them were serologically positive hence diagnosed with primary syphilis, secondary syphilis was diagnosed in 19 patients (24.1%) with constitutional symptoms such as fever accompanied by rash on the skin and palmoplantar rash, and the remaining 50 patients (63.3%) were asymptomatic thus considered as latent syphilis. In this study, we found 41 HIV coinfecting patients with other STI diseases such as genital herpes, condyloma acuminata, candidiasis vaginalis, and gonorrhoea. A total of 20

patients showed a single clinical symptom, while 9 patients showed multiple or more than 1 clinical symptoms.

Of the 79 cases, syphilis was latent in 50 patients. It is likely that symptoms of syphilis were mild, non-specific and did not cause complaints, making it difficult to make an early diagnosis. Data on risk factors and clinical manifestations are shown in **Table 2**.

### Laboratory data

Of 79 patients diagnosed with syphilis, RPR titers were 1:16 in 44 patients (55.7%) and 4 patients (5.1%) had higher titer 1:32. All syphilis cases were also screened for HIV infection in 41 HIV-infected patients, 26 of whom were MSM, 2 bisexual patients, 4 patients had sexual worker contact history. Laboratory data are shown in **Table 3**.

### Discussion

All cases with diagnosis of syphilis were the subject of this study. Some subjects were co-infected with other STI diseases such as HIV, genital herpes, candidiasis, condyloma, or gonorrhoea. The prevalence of syphilis has recently increased, hence more research is needed to improve health services in Makas-



sar. In this study, of all 79 cases of syphilis, the majority were men (79.7%) of whom 48.1% were homosexual/MSM, 2.5% were bisexual and 49.4% were heterosexual. The majority of transmission in heterosexual patients resulted from free sex and 5 female patients were infected by their (only one) partner. Syphilis is mostly diagnosed in men (51.8%) and young adults between the ages of 21 and 30 years. Subjects who were not married accounted for 55.7%. In 2014 the male population in the United States contributed to 90.8% of all cases of primary and secondary syphilis, the prevalence rates being highest at the age of 20 to 29 years. <sup>(1)</sup> The Centers for Disease Control and Prevention (CDC) reported that there was a rapid increase in the number of cases, with the largest increase in MSM and non-married men 60.2%, with homosexual and bisexual orientation (12). These findings vary from studies in Norway which reported that as many as 70% of heterosexual men were infected by their partners or sex workers, while in female almost half of them were infected by their sole partners (13). It is generally known that syphilis is mostly transmitted through sexual contact which is the most common transmission mode (9). Most of the syphilis patients are asymptomatic and thus diagnosed as latent syphilis, so according to our findings in this study, the predominant finding is latent syphilis. Patients who present with complaints of genital ulcers, sometimes accompanied by enlarged lymph nodes, are diagnosed with primary syphilis. Furthermore, secondary syphilis is diagnosed as the initial stage of syphilis among symptomatic patients. Some co-infected patients with other STI diseases have been observed. The distribution of RPR ranges from 1: 4 to 1:32 and the majority of patients in this study were found to have titers 1:16 (55.7%). HIV serology was positive in 51.9% of patients and 25 of them were MSM patients. Reported unprotected anal intercourse is increasing rapidly. Patients diagnosed with gonorrhoea, chlamydia or syphilis are more likely to be asymptomatic (14). Evaluation of recommendations for annual syphilis testing of HIV-positive MSM in the Netherlands revealed up to one-third of infections were asymptomatic and was detected by screening (15). Primary and secondary syphilis was mostly reported in the age group 15 to 19 and 20-39 in the Russian Federation and Kuala Lumpur, respectively (9, 13). In devel-

oping countries, up to 90% incidence of primary and secondary syphilis is reported in young men aged 20-29 years, but since 2006 the situation has changed so the most frequently infected are those aged 35-59 years (16). Studies in the United States reported that MSM, heterosexual men and HIV co-infected women had a higher risk of being infected with syphilis. They revealed up to 50% of MSM, who were diagnosed with syphilis, were also co-infected with HIV and around 61.1% of primary and secondary syphilis occurred among MSM (8, 17). Studies in China have also shown that increased prevalence of syphilis were detected among MSM and HIV-infected populations (18). Studies in Brazil also revealed similar findings, namely the existence of strong relationships between male gender and MSM orientation with higher *T. pallidum* infection (19). Various studies have shown similar findings in which MSM populations, male and young adults were the dominant group diagnosed with syphilis. Proper monitoring and testing of these high-risk populations can help to keep the disease under control (1). In this study, most patients showed no symptoms at the time of serological diagnosis thus making the diagnosis of latent syphilis dominant. This descriptive study encourages screening for all high-risk STI patients, where syphilis and HIV co-infection are a crucial matter to be explained further to the patients, especially in terms of treatment and prognosis.

## Conclusion

Our study showed there was a significant correlation between syphilis and an increased risk of HIV transmission in MSM groups. The higher number of cases of syphilis and HIV co-infection among MSM can increase transmission of both infections and should be considered a major risk factor for syphilis in Makassar.

## Abbreviations

CDC – Centers for Disease Control and Prevention  
FTA-ABS – Fluorescent treponemal antibody absorbed  
HIV – Human immunodeficiency virus  
IV – Intravenous  
MSM – Men who have sexual relationships with other men

RPR – Rapid plasma reagin  
 STI – Sexually transmitted infection  
 STBP – Surveilans terpadu biologi perilaku  
 SPSS – Statistical Package for Social Science  
 SD – Standard deviation  
 TPHA – Treponema pallidum haemagglutination  
 TRUST – Tolidine red unheated serum test  
 TPPA – Treponema pallidum particle agglutination

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## Sero-epidemiologija i faktori rizika sifilisa u Makasaru, Indonezija

### Sažetak

**Uvod.** Sifilis je infektivna bolest koju izaziva *Treponema pallidum* spirohete i uglavnom se prenosi seksualnim odnosom. Sifilis ima potencijal da izazove ozbiljne komplikacije i u tesnoj vezi je sa infekcijom HIV-om, zbog čega je sifilis veliki zdravstveni problem. U Indoneziji, pregledima visokorizičnih populacija koji su izvedeni 2007. i 2011. godine ustanovljeno je povećanje u rasprostranjenosti sifilisa, pogotovo kod homoseksualaca. Štaviše, u studijama su opisani faktori rizika za prenos HIV-a uključujući homoseksualne i heteroseksualne odnose, upotrebu droge intravenski i zaražene partnere. **Cilj** je bio utvrditi epidemiološke aspekte i faktore rizika za sifilis u Makasaru, kao i povezanost koinfekcije sa drugim seksualno prenosivim infekcijama. **Materijal i metode.** Ova studija je multicentrična, poprečnog preseka, deskriptivna sa konsekvativnim uzorkovanjem. Slučajevi su odabirani tako što je potvrđena dijagnoza

na osnovu seroloških rezultata dobijenih pomoću RPR, TPHA i HIV skrining testa. Slučajevi su analizirani na osnovu: epidemioloških karakteristika, faktora rizika i kliničkih nalaza, koinfekcije sa drugim seksualno prenosivim infekcijama i stadijuma bolesti. **Rezultati.** Bilo je ukupno 79 serološki potvrđenih slučajeva sifilisa u periodu između januara 2017. i decembra 2018. godine u Makasaru, glavnom gradu provincije Južni Sulawesi, Indonezija. Od 63 ispitanika muškog pola (79,7%), 38 (48,1%) bili su homoseksualci a od 41 slučaja ispitanika zaraženih HIV-om, 25 (60,9%) takođe su bili homoseksualci. **Zaključak.** Naša studija je pokazala da postoji značajna povezanost između sifilisa i povećanog rizika od prenosa HIV-a kod homoseksualnih grupa. Povećani broj sifilisa i HIV koinfekcije između homoseksualaca može povećati širenje obe infekcije i treba ga smatrati bitnim faktorom rizika za sifilis u Makasaru.

**Ključne reči:** Serodijagnoza sifilisa; Faktori rizika; Seroepidemiološke studije; Seksualno prenosive bolesti; Homoseksualnost muškaraca; Indonezija

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# Successful Management of Treatment-Resistant Alopecia Areata with Platelet Rich Plasma: A Case Series

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## Abstract

**Introduction.** Alopecia areata (AA) is an autoimmune disease-causing non-scarring alopecia. It is usually treated with immunosuppressive agents, to which some patients fail to respond adequately. **Material and Methods.** Three patients with AA refractory to standard therapy were treated with intra-dermal injection of autologous platelet rich plasma (PRP) every four weeks. **Results.** All three patients showed remarkable improvement after multiple sessions of PRP treatment. **Conclusion.** Autologous PRP is safe and effective in treatment-resistant forms of AA demonstrated in many case reports; therefore it deserves further study with randomized, placebo-controlled trials.

**Key words:** Alopecia Areata; Platelet-Rich Plasma; Treatment Outcome; Case Reports

## Introduction

Alopecia areata (AA) is an autoimmune disease ranging from a single patch of alopecia to alopecia universalis (1). It is usually treated with topical, intralesional and systemic immunosuppressive drugs (2). Since AA does not always respond to standard treatment, alternative therapies are required.

Platelet rich plasma (PRP) is a concentrate of autologous platelets widely used in various clinical disciplines to promote tissue regeneration. It is now emerging as a treatment for AA with minimal adverse effects (2).

We report the successful treatment of three challenging clinical presentations of alopecia areata with PRP.

## Case Reports

### Case 1

A 25-year-old female presented with AA (area of scalp hair loss approximately 75%), which has lasted for three years. She had been previously treated with topical steroids, 2% minoxidil lotion, dithranol paste, 0.1% tacrolimus ointment, intralesional triamcinolone and several courses of oral prednisolone, dexamethasone, azathioprine and sulfasalazine without success.

### Case 2

A 23-year old female presented with alopecia totalis lasting for 6 years. She had undergone topical treatments with steroids, 2% minoxidil lotion, dithranol paste, 0.1% tacrolimus ointment, intralesional triamcinolone, intravenous dexamethasone pulses, oral prednisolone, and sulfasalazine. By the time she presented to us there was no progression of the hair loss but there was no new hair growth.

### Case 3

A 55-year-old female presented with alopecia totalis lasting for 4 years. She was treated with topical steroids, dithranol paste, 0.1% tacrolimus ointment, intralesional triamcinolone acetone injections, oral prednisolone, intravenous dexamethasone pulses, sulfasalazine and oral methotrexate.

As stated above a fair trial of the available treatment protocols was attempted; however, in spite of it there was continued progression and despite regrowth of hair it was followed by a relapse of symptoms. We treated these three patients with autologous PRP as mentioned below.



**Figure 1.** Prior to commencement of therapy and following commencement of therapy

### Material and Methods

Their basic haematological and biochemical investigations were within the normal range. Their thyroid functions were normal and thyroid antibodies were negative. They had no other co-morbidities.

PRP was prepared using 40ml of each patient's blood using sodium citrate (9:1) as the anticoagulant. Centrifugation was carried out at 3000 rpm for ten minutes followed by 2000 rpm for five minutes. A total volume of about 10ml of PRP was injected intradermally to the bald patches on the scalp 1cm apart under regional anaesthesia with lignocaine and adrenaline (2% lignocaine with adrenaline 1:80 000 at a dose of 7 mg/kg with roughly around 15 ml of lignocaine diluted up to 20 ml with distilled water was used). The procedure was repeated every four weeks until a satisfactory response was obtained.

During the PRP treatment, the patients were advised to apply 5% minoxidil lotion and topical steroids. No systemic therapy was used.

The treatment was well tolerated by all three patients without side effects. The response to treatment was monitored with global photographs of the scalp at each visit. At the end of the third session, case 1 had showed a marked response with approximately 80% recovery of scalp hair growth (**Figure 1**). Case 2 and case 3 demonstrated almost complete recovery of scalp hair growth after the sixth and eighth sessions, respectively.

### Discussion

Alopecia areata (AA) is an autoimmune disease targeting anagen hair follicles leading to non-scarring alopecia ranging from being relatively mild with some patches of hair loss to total loss of scalp (alopecia totalis) and

body hair (alopecia universalis). It is usually treated with corticosteroids (intralesional, topical and oral), contact immunotherapy, minoxidil and immunosuppressive drugs. Some patients do not respond to any of the above treatment modalities.

PRP is an autologous platelet concentrate suspended in plasma. It is used in many clinical disciplines to promote tissue regeneration. Amongst more than 20 growth factors (GFs) present in PRP, platelet-derived growth factor (PDGF), transforming growth factor- $\beta$  (TGF- $\beta$ ) and vascular endothelial growth factor (VEGF) are mainly responsible for the regenerative action (3).

These GFs bind to receptors of stem cells located in the bulge area of the hair follicles and promote their transformation to hair follicular cells (4). They also cause proliferation of dermal papillary cells (3). The end result is activation and continuation of the anagen phase of the hair cycle (4, 5). PDGF and VEGF have angiogenic potential and improve perfusion to hair follicles (6). PRP can be used alone or in combination with other treatment methods (3).

Several randomized, double blind, placebo-controlled, half-head studies in patients with AA have demonstrated increased hair growth after treatment with PRP without major adverse effects. As the effectiveness of PRP

in treatment-resistant forms of AA has been demonstrated mainly in case reports, it deserves further study with randomized, placebo-controlled trials. As of now, PRP may be offered as a new and potentially successful treatment for patients with AA who fail to respond to standard therapy (7).

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## Primena plazme obogaćene trombocitima u uspešnom lečenju alopecije areata otporne na tretman – prikaz serije slučajeva

### Sažetak

**Uvod.** Alopecija areata je autoimuno oboljenje koje izaziva alopeciju bez ožiljaka. Obično se leči imunosupresivnim agensima na koje neki pacijenti ne reaguju adekvatno. **Materijal i metode.** Tri pacijenta sa alopecijom areata, koji nisu reagovali na standardnu terapiju, lečeni su intradermalnim ubrizgavanjem autologne plazme obogaćene trombocitima svake četiri nedelje. **Rezultati.** Kod sva tri pacijenta je došlo do primetnog pobolj-

šanja posle višestrukih tretmana plazmom obogaćenom trombocitima. **Zaključak.** Autologna plazma obogaćena trombocitima je bezbedna i efikasna u lečenju onih oblika alopecije areata koji su otporni na lečenje, kao što je pokazano u mnogim prikazima slučajeva i stoga zaslužuje dalje istraživanje u okviru studija sa slučajnim uzorkom i placebo kontrolom.

**Ključne reči:** Alopecija areata; Plazma bogata trombocitima; Ishod terapije; Prikazi slučajeva

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# Bacterial Vaginosis in Pregnant Women at Maternal and Child Hospital, West Java, Indonesia, 2018: High Prevalence in Asymptomatic Females

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## Abstract

Bacterial vaginosis (BV) is a lower genital tract infection of reproductive women which can occur in pregnant and non-pregnant women. BV in pregnant women can increase the risk of complications, including increased incidence of abortion, premature rupture of membranes, preterm birth, and babies with low birth weight. BV can also increase the risk of acquired sexually transmitted infection (STI) and their further transmission, including human immunodeficiency virus (HIV). Each country has a different prevalence of BV. The previous report of BV prevalence in pregnant women was submitted in Jakarta, Indonesia in 1990. Until now, there is no update data of BV in pregnant women, especially in West Java, Indonesia. Thus, we conducted a descriptive observational study using a cross-sectional design and a consecutive sampling method in June 2018. This study included 60 pregnant women in the Maternal and Child Hospital, Bandung, Indonesia. Out of 60 participants, seven (11.67%) participants had BV according to Amsel criteria. Asymptomatic BV was diagnosed in all participants. This study shows the prevalence of BV in pregnant women in the Maternal and Child Hospital in Bandung during June 2018. The assessment of screening BV should be recommended as a routine workup. To avoid complications in pregnant women and infants it should not be waited for the symptoms to reveal.

**Key words:** Vaginosis, Bacterial; Reproductive Tract Infections; Pregnancy Complications, Infectious; Prevalence; Asymptomatic Infections; Indonesia

## Introduction

Bacterial vaginosis (BV) is a polymicrobial clinical syndrome, occurring in the lower genital tract of women of reproductive age in both non-pregnant and pregnant women (1). BV occurs due to an imbalance of normal vaginal flora in the vagina, *Lactobacillus* spp. which is the main vaginal normal flora, replaced mostly by anaerobic bacteria (2), such as *Gardnerella vaginalis* (*G. vaginalis*), *Mobiluncus* sp., and *Mycoplasma hominis* (*M. hominis*) (2, 3). The prevalence of BV in each country varied in meta-analysis studies performed from 1984 to 2010 in England, Spain, Serbia, Canada, Unit-

ed States of America, Peru, Iran, and China. In this meta-analysis study the prevalence of BV in pregnant women ranged from 4% to 48.7%, and in non-pregnant women from 11.1% to 60.8%. The prevalence of BV in pregnant women in several Asian countries was 7.5% (the Philippines), 12.5% (Thailand) and 22% (Laos) (4). A study including 490 pregnant women from three hospitals in Jakarta was conducted to assess the prevalence of BV in pregnant women and BV was reported in 17% of pregnant patients (5). Until now, data on BV prevalence in pregnant women have not been updated, especially in West Java, Indonesia.

## Material and Methods

### Study Subjects

This study included 60 pregnant women aged 17-40 years using consecutive sampling method. The exclusion criterion was the patient with pervaginal bleeding at the moment of coming to the hospital.

### Study Design

It was a cross-sectional study carried out at the Obstetrics and Gynecology Clinic at Maternal and Child Hospital, Bandung, West Java, Indonesia in June 2018. All the patients were subjected to careful history taking, physical examination, and laboratory examination. Sociodemographic data, sexual behavior characteristics, obstetric and gynecological characteristics, and Amsel criteria characteristics were assessed.

### Ethical Considerations

Information of the participants was kept confidential. The study was approved by the Ethical Committee of Dr. Hasan Sadikin Hospital, affiliated with Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.

### Results

Out of 60 pregnant women from this study sample, seven (11.67%) were diagnosed with BV and they fulfilled Amsel criteria. Based on the sociodemographic characteristics and behavior, five out of 28 study participants who were diagnosed with BV were >30 years old. Then, one in four study participants with junior high school education was diagnosed with BV. Meanwhile, out of 53 study participants who were housewives, seven were diagnosed with BV. Then, one study participant who had a frequency of sexual intercourse more than once per week was diagnosed with BV. BV diagnosis was based on all sociodemographic characteristics and behavior of the study participants. Based on the characteristics of the obstetric and gynecological history, two out of nine study participants in the first trimester of pregnancy were diagnosed with BV in this study. Two out of 37 participants in the second trimester of pregnancy were diag-

nosed with BV. Three out of the 47 study participants in the third trimester of pregnancy were diagnosed with BV. There was no history of abortion, premature rupture of membranes, and a history of low birth weight babies (LBWB) in the study participants with BV.

The results of BV examination in patients participating in the study were based on Amsel criteria. All study participants were asymptomatic. Venereological examination revealed homogeneous vaginal discharge in 17 study participants, seven of whom were diagnosed with BV. Examination of vaginal pH > 4.5 was found in 10 study participants, seven of whom had BV. The result of positive Whiff test and clue cells were found in all examined study participants diagnosed with BV.

### Discussion

Bacterial vaginosis is one of the main causes of vaginitis in women of reproductive age, and more than 50% of pregnant women with BV are asymptomatic (2, 3). Matic et al. (6) conducted a study in 2014, which included 111 pregnant women who had ante natal care (ANC) in the Military Medical Academy, Serbia, and found that all of pregnant women with BV were asymptomatic. In a meta-analysis study conducted by Leitich et al. (7) out of 10,286 pregnant women, all with BV were asymptomatic. In this study, seven out of 60 pregnant women were diagnosed with BV.

Prevalence of BV in this study was 11.67% out of 60 pregnant women. The prevalence of BV in pregnant women varies in many studies. A study conducted by Ridwan et al. (5), including 490 pregnant women who had ANC at three hospitals in Jakarta found the prevalence of BV to be 17%. While, in the study conducted by Thammalangsy et al. (8) in 500 pregnant women who came to the ANC the BV prevalence was 14.4%. In the study conducted by Lata et al. (9), the prevalence of BV was 20.5% 200 pregnant women who had ANC. Furthermore, in the study conducted by Shresta et al. (10) it was revealed that 78 pregnant women had BV (52.6%). Machado et al. (11) found that the prevalence of BV was 3.88% in 206 pregnant women who had ANC. In a study conducted by Matic et al. (6) in 2014, the prevalence of BV was 26.1% in 111 pregnant women who had ANC.



**Table 1.** Characteristics of sociodemography and sexual behaviour in participants with positive BV

Characteristics	Positive BV		
	n = 60	Total	Proportion
<b>Age</b>			
<30 years old	32	2	2/32
> 30 years old	28	5	5/28
<b>Education</b>			
Elementary school	6	0	0/6
Junior High school	4	1	1/4
Senior High school	30	5	5/30
College	20	1	1/20
<b>Occupation</b>			
Government officer			
Teacher in junior high school	1	0	0/1
Nurse	1	0	0/1
Private employee			
Textile factory	3	0	0/3
Wedding organizer	1	0	0/1
House wife	54	7	7/54
<b>Sexual behaviour</b>			
<b>Coitarche</b>			
16-20 years old	2	1	1/2
>20 years old	58	6	6/58
<b>Frequency of sexual intercourse</b>			
≥ 1/month	13	0	0/13
1/week	46	6	6/46
> 1/week	1	1	1/1

Various BV cases were influenced by several factors including genetics (12), smoking (13), vaginal douching (13, 14), coitarche (14), and higher frequency of sexual intercourse (15). In this study, all participants had vaginal pH >4.5, seven participants were diagnosed with BV. pH was <4.5 in 50 participants out of 53 study participants who were not diagnosed with BV. Thomason et al. (16) found that the sensitivity and specificity of vaginal pH of women who had BV were 81.6% and 87.7%, respectively. Nelman et al. (17) found that the sensitivity and specificity of vaginal pH examination in women with BV was 86% and 96%, respectively. Vaginal wall examination revealed the presence of clue cells > 20% in BV

patients. Thomason et al. (16) found that the sensitivity and specificity of clue cells in women who experienced BV were 89.8% and 98%, respectively. Similar results were obtained in the study of Nelman et al. (17), i.e. the sensitivity and specificity of clue cells in women who had BV was 82% and 96%, respectively. The characteristics of BV were related to sociodemography, sexual behavior, and age. Out of 32 study participants who were aged <30 years, two had BV. The similar result was reached in the studies conducted by Machado et al. and Octaviyati et al. (11, 18). A study conducted by Machado et al. (11) in 2014, including 206 pregnant women who had ANC at Braga Hospital, Portugal, revealed that in

**Table 2.** Result of BV in participants based on Amsel criteria

Characteristic Amsel criteria	Total n = 60	Total %
<b>Vaginal discharge*</b>		
No	43	71.67
Yes	17	28.33
If yes		
Characteristic discharge of BV**	17	28.33
Whiff test		
Positive	7	11.67
Negative	53	88.33
<b>pH vagina</b>		
> 4,5	10	16.67
< 4,5	50	83.33
<b>Clue cell</b>		
Yes	7	11.67
No	53	88.33
Amsel criteria > 3	7	11.67

\*Vaginal discharge based on venereological examination

\*\*Characteristic discharge of BV including white or grayish colour, with homogenous consistency

women > 30 years old the risk of getting BV was five times higher, with odd ratio (OR) 5.27; 95% CI. In a study conducted by Octavianti et al. (18), for 492 women in several Primary Health Care unites in Indonesia, it was known that women over the age of 40 had three times higher risk of developing BV (OR 3.15, 95% confidence interval (CI)), with statistically significant  $p < 0.05$ . Different results were obtained in the study conducted by Nwadioha et al. (19), it was found that the highest age group that had BV was <30 years old, which was an active sexual age. This is speculated to be related to sexual activity due to semen that has a pH of 7,2. It may affect the normal balance of vaginal flora (20). The increasing vaginal pH will decrease the Lactobacillus spp., hence the growth of anaerobic bacteria increases (19, 20).

The dynamics of vaginal microflora is affected by age. As we get older, estrogen production decreases (hypoestrogens), resulting in a decrease in glycogen production in vaginal epithelial cells (21). Glycogen is a nutrient needed by Lactobacillus spp. to produce lactic acid which maintains the acidity of vaginal pH

and controls the growth of anaerobic bacteria, thus preventing the occurrence of BV (22). Hence, it explained higher occurrence of BV in the age group >30 years old.

In this study, one in four study participants from 20 research participants had a college education level and suffered from BV. All study participants who had high elementary education did not have BV. In research conducted in developing countries, BV is generally more prevalent in participants with high school level education. Similar results were obtained in the study conducted by Ocviyanti et al. (18) in 492 women, in several Puskesmas in Kerawang, Pedes, Cikampek, Tempuran, and Batalion Clinic, in Indonesia, i.e. the highest number of BV patients had high school education (46.3%). A study conducted by Tachawatcharapunya et al. (23) in Thailand found that women with the highest number of BV had high school education (97.8%), but the results were not statistically significant ( $p > 0.05$ ). In the study conducted by Shahgelbi et al. (24), it was found that the education of women who experienced the highest number of BV was at the high school level. In studies

in developed countries, the level of education of women who experience BV also varies as in studies conducted by Kouman et al. (25), Allworth et al. (26), and Billard et al. (27) In studies conducted by Kouman et al. (25) and Allworth et al. (26) 2001 it has been shown that most women who experienced BV were with junior high school education. On the other hand Bilard et al. (27) have reported that the highest level of education of women with BV is diploma. The level of education of women with BV in previous studies varied. So based on these studies, it is necessary to conduct further studies on the influence of education level on BV risk factors in Indonesia.

According to the study participants, out of 54 housewives, seven (12.96%) experienced BV. The study conducted by Ocviyanti et al. (18), revealed that 69.2% out of 492 women in Indonesia who had BV were housewives. In a study conducted by Thammalangsy et al. 64.4% of 500 pregnant women who had ANC and were diagnosed with BV were housewives. In the study conducted by Siahaan et al. (28) of 117 women in Manado, Indonesia, 35.8% were housewives. The higher prevalence in housewives may be explained by the fact that they have more free time to seek consult (28). This can explain the results of this study, although further research is needed. The Siahaan study was supported also by other studies conducted by Tachawatcharapunya et al. (23) in Thailand and Ocviyanti et al. (18) in Indonesia, it is known that most patients diagnosed with BV are housewives.

Bacterial vaginosis relates to various sexual behaviors including coitarche at a young age (14, 15). In this study based on the characteristics of coitarche, one in two study participants aged 16-20 years was diagnosed with BV. In a study conducted by Fether et al. (14) at Melbourne University, 528 female students had BV and 120 patients (22.2%) had history of coitarche at age <16 years old. In this study, BV patients mostly had coitarche at a young age (<16 years old) that being statistically significant.

The frequency of sexual intercourse is one of the risk factors for BV (15). In this study, six out of 46 study participants who were sexually active once a week had BV. Study participants who were sexually active had a frequency of sexual intercourse more than once

a week. While, all of the study participants who had a frequency of sexual intercourse once a month had no BV. The increase in the incidence of BV against the frequency of sexual intercourse was thought to be caused by alkaline semen with a pH of 7.2 (20) so that *G. vaginalis* became dominant after coitus (15, 29).

In this study, out of nine participants in the first trimester of pregnancy, two experienced BV. Out of 37 study participants in the second trimester of pregnancy, two developed BV. However, out of the 14 study participants in the third trimester of pregnancy, three developed BV. In the study conducted by Nelson et al. (30) it is known that the women in the third trimester are more likely to develop BV. Similar with the study conducted by Machado et al. (11), BV mostly occurred in the second trimester of pregnancy. However, in the study conducted by Kirakoya et al. (31), it occurred within the first trimester of pregnancy. Based on multivariate analysis conducted by Machado et al. (11) there was no relationship between BV and the trimester of pregnancy ( $p=0.27$ ). The results of a similar multivariate analysis were obtained in the study of Kirakoya et al. (31). that BV relationship with gestational age was not statistically significant. While in another study, BV positive study participants with history of abortion, prematurity (32, 33). LBWB, and premature rupture of membranes (PROM) (33) were found to have no history of pregnancy. The results of this study are different from other studies in the positive BV group who had history of pregnancy complications.

## Conclusion

The prevalence of BV in pregnant women at Maternal and Child Hospital, West Java, Indonesia was 11.67%. The assessment of screening BV should be recommended as a routine workup. To avoid complications in pregnant women and infants it should not be waited for the symptoms to reveal.

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## Bakterijska vaginoza kod trudnica u Bolnici za majku i dete, Zapadna Java, Indonezija, 2018 – visoka prevalencija bez simptoma

### Sažetak

Bakterijska vaginoza je infekcija donjeg genitalnog trakta žena u reproduktivnom dobu, koja se može pojaviti kod trudnica i kod žena koje nisu trudne. Bakterijska vaginoza kod trudnica može povećati rizik od komplikacija, uključujući i povišenu incidenciju abortusa, prerane rupture membrana, porođaj pre vremena i malu težinu novorođenčeta. Takođe može da poveća rizik od stečenih i prenetih infekcija koje se prenose seksualnim putem, uključujući i virus humane imunodeficijencije. Svaka država ima različitu prevalenciju bakterijske vaginoze. Pre skoro tri decenije, izveštaj o prevalenciji bakterijske vaginoze kod trudnica je podnet u Džakarti (Indonezija) 1990. godine. Do sada nije bilo ažuriranih podataka o bakterijskoj vaginozi kod trudnica, pogotovo

ne u Zapadnoj Javi (Indonezija). Stoga smo mi u junu 2018. godine sproveli deskriptivnu opservativnu poprečno-presečnu studiju koristeći metod konsekutivnog uzorkovanja. Ova studija je uključila 60 trudnica iz Bolnice za majku i dete u Bandungu (Indonezija). Od 60 učesnica, sedam (11,67%) ih je imalo bakterijsku vaginozu prema Amsel kriterijumima. Asimptomatska bakterijska vaginoza je dijagnostikovana kod svih učesnica. Ova studija pokazuje prevalenciju trudnica u Bolnici za majku i dete u Bandungu juna 2018. godine. Procenu skrininga bakterijske vaginoze bi trebalo preporučiti kao rutinski postupak. Da bi se izbegle komplikacije kod trudnica ne treba čekati da se pojave simptomi.

**Ključne reči:** Bakterijska vaginoza; Infekcije reproduktivnog trakta; Infektivne komplikacije u trudnoći; Prevalencija; Asimptomatske infekcije; Indonezija

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# Unilateral Mediothoracic Exanthem: Case Reports of two Indian Female Children

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## Abstract

Unilateral mediothoracic exanthem is a variant of a common entity in Western literature, namely Asymmetric Periflexural Exanthem of Childhood (APEC). Less than ten cases of unilateral mediothoracic exanthem have been described worldwide, and only two are reported in Indian literature. Herein, we report two childhood cases of unilateral mediothoracic exanthem from India. Dermatologists must be aware of this self-limiting condition, in order to avoid invasive and exhaustive investigations and misdiagnosis.

**Key words:** Exanthema; Skin Diseases; Child; Thoracic Wall; Diagnosis; Treatment Outcome; India; Histamine Antagonists

## Introduction

Asymmetric periflexural exanthem of childhood (APEC), a distinctive clinical entity usually seen in Caucasian children, is characterised by the acute onset of unilateral pruriginous erythematous rash, which may be maculopapular, micropapular, scarlatiniform or eczematous. It classically involves the flexures (axilla or groin) initially and later on, progresses centrifugally to involve trunk and extremities. The rash may become bilateral in later course of the disease (1, 2).

APEC is usually preceded by a prodrome of low-grade fever and involving upper respiratory tract or gastrointestinal tract. The general health of the child remains unaffected. It may be associated with regional lymphadenopathy. Spontaneous remission occurs in about 3 to 6 weeks (1–3).

A variant of APEC, namely unilateral mediothoracic exanthem (UME), is not periflexural in onset and usually touches the midline in contrast to APEC, where the rash being periflexural does not touch the midline (4). Only a handful of cases of UME have been described so far in worldwide literature (3, 5). To the best of our knowledge, the only cases described from India were in a 16-year-old adolescent boy and a 35-year-old female (5). Herein, we are reporting two childhood cases

of UME from North India. Ours are the only childhood cases of UME in Indian literature.

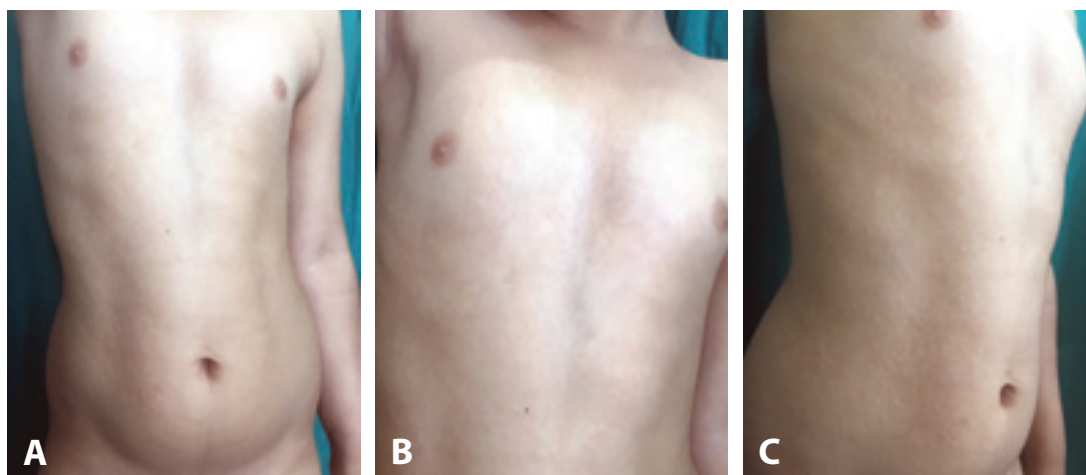
## Case studies

### Case 1

A six-year-old female child presented with slightly itchy, skin coloured to reddish eruption affecting the right side of her body for five days duration. The rash began suddenly on her right chest and then progressed down to involve the same side of abdomen and right thigh.

The rash was not associated with pain, fever, constitutional symptoms, upper respiratory or gastrointestinal infection. There was no history of similar rash in siblings or parents. Any exposure to chemicals, sand, topical preparation, or pets was absent. Drug history was unremarkable. No triggering or precipitating factor was identified. The child was otherwise in good general health.

On cutaneous examination, micropapular skin coloured to erythematous exanthem was noted on the right half of chest and abdomen, which was strictly unilateral and stopped abruptly at the midline (**Figure 1 A**). It extended to the right lower limb as well; however, axilla and groin remained uninvolved (**Figure 1 B**). The rash was confluent and ec-



**Figure 1.** A). Skin coloured to erythematous rash on the right half of trunk, abruptly stopping at the midline. B). Unilateral medi thoracic exanthem sparing the axilla. C). The right half of trunk; unilateral exanthem is confluent and eczematous on the abdomen

zematous on the abdominal area (**Figure 1 C**). Vesicles, purpura and petechiae were absent. It was not associated with regional lymphadenopathy. Systemic examination revealed no abnormality.

Routine blood investigations, C-reactive protein and ASO titres were within normal limits. Serology for parvovirus B19, Epstein-Barr virus, cytomegalovirus, adenovirus, hepatitis B and C viruses were negative. The parents of this child did not give consent for skin biopsy. Based on history, distinctive distribution of rash, and investigations, the diagnosis of unilateral medi thoracic exanthem (UME) was made. Oral antihistamines and bland emollients were advised. Complete remission was noted within three weeks of the onset of rash.

#### Case 2

A five-year-old female came with complaint of asymptomatic skin coloured papular eruption on the left half of chest and abdomen for about a week. The rash also progressed to the left thigh, but never involved axilla, groin or contralateral half of body (**Figure 2 A and B**). Vesicles and purpura were not found.

There was no history of fever, upper respiratory or gastrointestinal infection. Family history was unremarkable. No triggering factors, for instance, chemicals, sand, topical or oral drugs were identified. General health was good and systemic examination revealed no abnormality. Lymphadenopathy was absent.

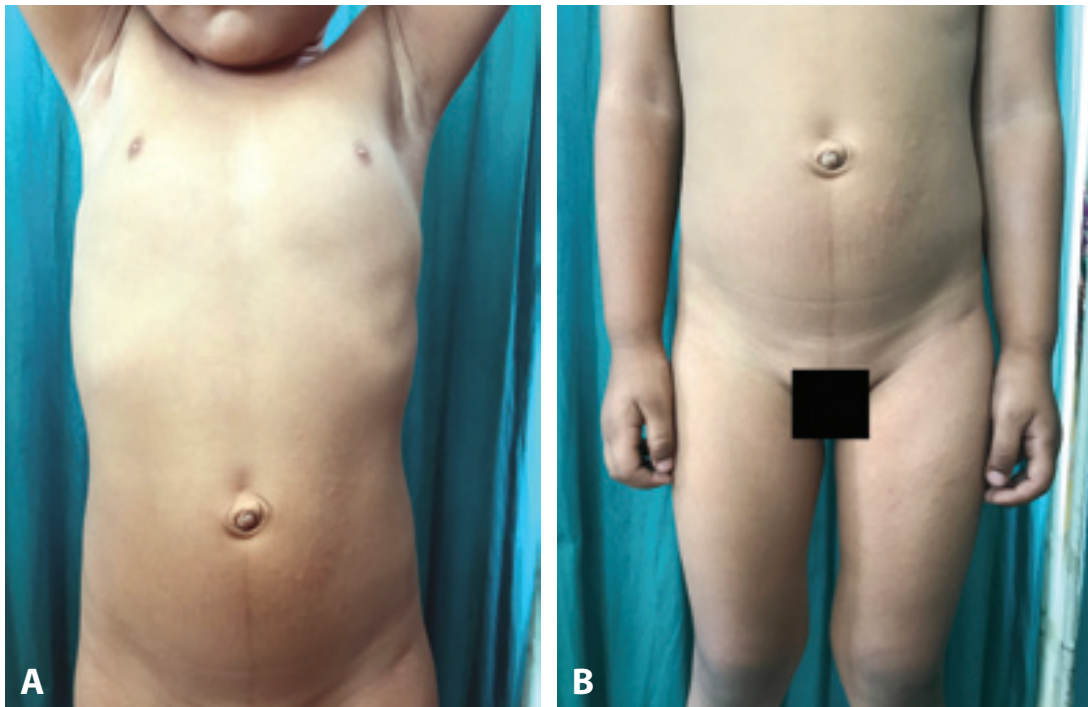
Blood chemistry, C-reactive protein, urine examination, ASO titres were within normal limits. Viral markers were negative. Consent for skin biopsy was not given by her parents. The clinical diagnosis of UME was made and oral antihistamines and emollients were prescribed. The rash subsided within four weeks of its onset.

#### Discussion

In 1962, Brunner et al. (6) described a distinct eruptive disorder with unilateral periflexural distribution, under the heading "A new papular exanthem of childhood". Similar exanthem was called as "Localised erythema with regional lymphadenopathy" by Taieb et al. in 1986, which they renamed as APEC (Asymmetric periflexural exanthem of childhood) in 1993. (7). In 1992, Bodeman and deProst proposed the term "unilateral latero-thoracic exanthem (ULM)", based on the most common site of this rash (8). Since then, numerous cases of ULM/ APEC have been described in Western literature, mainly from France and Italy (1). However, its variant, unilateral medi thoracic exanthem (UME), is a rare disease, with only a couple cases reported from India (5).

Unilateral exanthem usually occurs in Caucasian children of age group 1-5 years, with male to female ratio 1:2. There is a seasonal predilection from February to September. Human transmission is not noted. Al-





**Figure 2.** A). Unilateral mediothoracic exanthem on the left half of the trunk without axillary involvement. B). Unilateral exanthem extending to the left thigh without involving groin

though several authors have hypothesised the role of viral aetiology, inoculation with *spiroplasma species*, or a link to pityriasis rosea in the pathogenesis of this exanthem, the real aetiology remains unproven (1). The unilateral predominance of the eruption may be explained by a post zygotic mutation at an early stage of embryogenesis, which renders the keratinocytes of one side of body more reactive to infective agents (9).

During the evaluation of the present cases, other differential diagnoses were ruled out on the basis of history and clinical examination. Herpes zoster was unlikely as there were no vesicles throughout the course of the disease and the rash was not painful. Atypical pityriasis rosea and Gianotti Crosti syndrome were unlikely. Gianotti Crosti syndrome causes a brownish-red rash that is symmetrical and typically involves the cheeks, buttocks, forearms, and legs. It generally does not affect the trunk. Irritant and allergic contact dermatitis were ruled out as detailed history did not reveal any potential irritants or allergens. History also excluded drug related rash, including over-the-counter topical or systemic drugs, and topical and systemic remedies.

Histopathology of unilateral exanthem reveals mild to moderate mononuclear interface dermatitis and mononuclear infiltrate in dermis, with clear predominance around sweat glands (perisudoral infiltrate) (10). This is quite typical of unilateral exanthem, and not seen in any of the above differential diagnoses. In our cases, skin biopsies were not performed due to lack of parents' consent.

Our case reports warrant attention due to paucity of cases of unilateral exanthem in Indian literature. Lack of reports also suggests possibilities of misdiagnosis and under-reporting by Indian clinicians. Inability to clinically diagnose unilateral exanthem leads to exhaustive, expensive and invasive workup. Therefore, we urge the dermatologists to become aware of this self-limiting entity in order to avoid a wrong diagnosis and unnecessary investigations.

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## Unilateralni mediotorakalni egzantem: prikaz dva slučaja indijskih devojčica

### Sažetak

Unilateralni mediotorakalni egzantem je jedna varijanta čestog entiteta u zapadnjačkoj literaturi, naime asimetričnog perifleksuralnog egzantema u detinjstvu. U svetu je opisano manje od deset slučajeva unilateralnog mediotorakalnog egzantema, a samo dva su objavljena u

indijskoj literaturi. Ovde prikazujemo dva slučaja unilateralnog mediotorakalnog egzantema u detinjstvu iz Indije. Dermatolozi moraju biti svesni ovog oboljenja kako bi izbegli invazivna i isrpjujuća ispitivanja i pogrešnu dijagnozu

**Ključne reči:** Egzantem; Kožne bolesti; Dete; Torakalni zid; Dijagnoza; Ishod terapije; Indija; Histaminski antagonisti

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# DERMOSCOPY OF THE MONTH

## Recurrent Vulvar Melanoma – a Case Report

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### Abstract

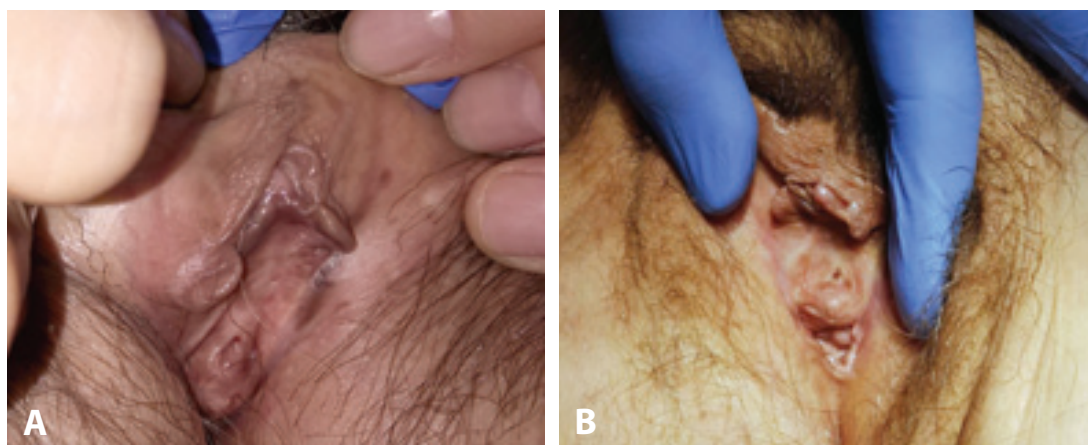
Melanoma rarely develops in the genital area. It is responsible for 5% of all vulvar malignancies. Postmenopausal women are usually more affected and the main differential diagnosis is vulvar melanosis and vulvar nevi. There are limited numbers of studies on dermoscopic features of mucosal melanoma, particularly early-stage lesions. Dermoscopic criteria have been described for the diagnosis of vulvar melanosis, and observational studies have been conducted to define the dermoscopic features of nevi and melanoma on the vulva. We are presenting the case of a 69-year old female with suspected recurrence of vulvar melanoma who previously had surgical removal of mucosal lentiginous melanoma on the left labia minor in June 2017. Five months after the primary melanoma surgery, the patient noticed de novo pigmentation at the left and right labia minor and urethral opening. On clinical examination, irregular light-brown pigmentation with ill-defined borders was evident on the labia minora of the vulva and around the external urethral orifice. On dermoscopy, irregular pigmented network, with white scar-like and structureless pinkish areas was evident. Incisional biopsy of the vulvar mucosa revealed melanoma in situ, confirming the local recurrence. CT scans of the head, thorax, abdomen and pelvis and gynaecological examination revealed no secondary deposits. Ultrasound of the regional inguinal lymph nodes revealed enlarged suspected pathologic involvement of the lymph nodes in both inguinal regions. Lymph node fine needle aspiration of lymph nodes in the left and right inguinal area revealed pleomorphic infiltrate of lymphoid cells with hemosiderin or melanoma pigment in the cytoplasm. Cystoscopic findings were within normal range. Interdisciplinary tumour board indicated wide excision of melanoma with margins of 1 cm and resection of the urethra, as well as biopsy of the enlarged left inguinal lymph node. Histopathological analysis of the resected mucosa revealed lentiginous spread of melanocytes showing moderate atypia, with focal pagetoid spread, without mitoses and ulceration and without invasion of lamina propria. The resection margins were tumour-free. Non-specific lymphadenitis was diagnosed on lymph node histopathological analysis. The patient was regularly monitored by a dermatologist and urologist, and had no recurrence. The accurate and prompt diagnosis is essential in the case of the vulvar melanoma which has unfavourable and unpredictable prognosis, with a tendency of local recurrences and regional and distant metastases in the case of invasive melanoma. In order not to miss early mucosal melanoma, dermatologists and gynaecologists should not avoid biopsy of lesions that demonstrate any clinical or dermoscopic feature of atypical melanocytic lesion, especially in case of the development of irregular pigmentation that expands and changes over time, the appearance of a solitary amelanotic papule or nodule requires excision or, in case of large diameter lesions, incision biopsies. Larger studies are needed to define more rigorously clinical and dermoscopic criteria that accurately distinguish early mucosal melanomas from benign skin lesions.

**Key words:** Vulvar Neoplasms; Melanoma; Dermoscopy; Diagnosis; Neoplasm Recurrence, Local; Case Reports

### Introduction

Genital pigmented lesions are a diagnostic challenge because a differential diagnosis

includes nevus, genital melanotic macules (lentiginosis, melanosis), angiokeratoma, seborrheic keratosis, squamous cell carcinoma

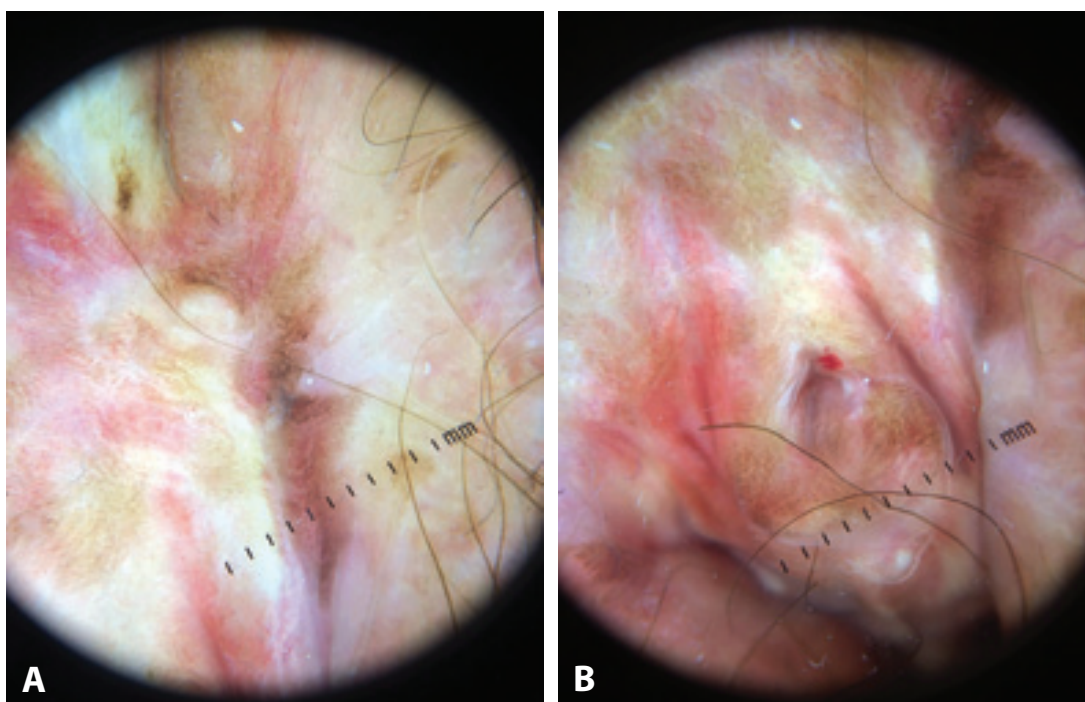


**Figure 1 a and b.** Irregular light to dark brown pigmentation was present on the left and right labia minora, spreading to the urethral orifice

(SCC), basal cell carcinoma (BCC) and melanoma. Genital melanoma and vulvar melanoma, in particular, is a rare entity. It is responsible for 5% of all vulvar malignancies (1). Mucosal melanoma is a rare disease, accounting for approximately 1.4% of all melanomas and only 0.03% of all new cancer diagnoses (2-4). Mucosal melanomas arise from mucosal epithelium anywhere but are most commonly found in three areas; the vulvov-

gina (18% of cases), the anorectum (24% of cases) and the oral cavity, nasal cavity or sinuses (55% of cases) (5). Vulvar melanoma more frequently occurs in postmenopausal women, and long-term prognosis is poor due to the high rate of recurrence (6, 7).

Dermoscopy is a non-invasive tool that helps physicians to distinguish melanomas from other pigmented and non-pigmented skin lesions. Dermoscopic criteria have been described for the



**Figure 2 a and b.** Melanocytic lesion: irregular pigmented network, with white scar-like and structureless pinkish areas was evident

diagnosis of vulvar melanosis, and observational studies have been conducted to define the dermoscopic features of nevi and vulvar melanoma, but clinical and dermoscopic differentiation between melanoma and melanosis is difficult (8-11).

In this article, we present a case of recurrent vulvar melanoma in a 69-year old Caucasian female.

### Case Report

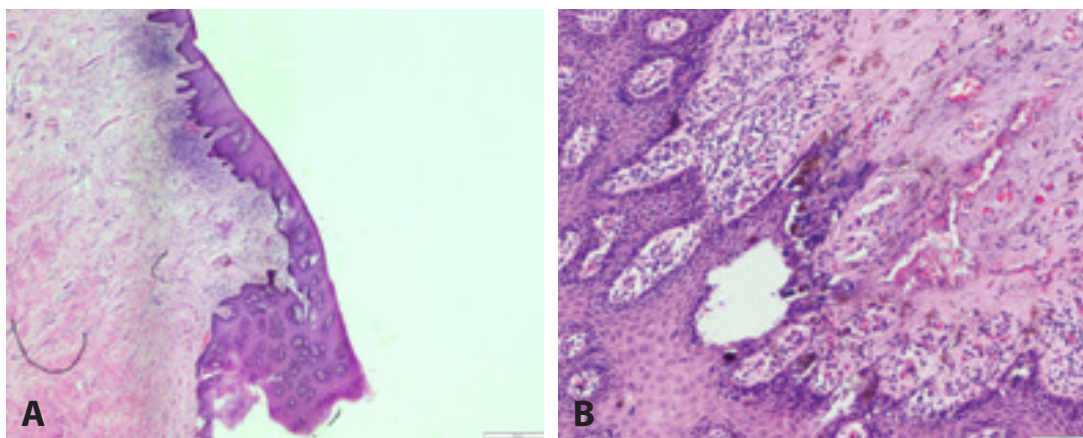
A 69-year old female, without a family history of skin cancer, was admitted to our Clinic to be examined for suspected recurrence of vulvar melanoma. In June 2017, mucosal lentiginous melanoma was excised on the left labia minor, and histopathology revealed melanoma in situ. On immunohistochemistry, SOX-10, Melan-A, HMB-45 were continuously expressed along the basal layer, focally in nests and in a suprabasal layer, with one HMB 45+ cell in superficial dermis, suggesting invasion. Abdominal and pelvic magnetic resonance imaging (MRI) in October 2017, showed postoperative sequelae with no signs of recurrent disease. In November 2017, light-brown irregular pigmentation appeared again, biopsy was done and on histopathology lentiginous melanocytic hyperplasia with mild and moderate atypia was described.

In the further months, pigmentation spread to the left and right labia minor area, involving external urethral orifice. A gynecologist referred the patient to the dermatologist for clinical examination and dermoscopy. On admission the patient complained of difficulty in urinating.

On clinical examination, irregular light to dark brown pigmentation was present on the left and right labia minora, spreading to the urethral orifice (**Figure 1a and 1b**). On dermoscopy, irregular pigmented network, with white scar-like and structureless pinkish areas was evident (**Figure 2a and 2b**).

**Regular laboratory analyses** including complete blood count, biochemistry, liver function tests, complete urinalysis, LDH, and protein S100, were all within normal range. Regional inguinal lymph node ultrasound examination revealed enlarged suspected pathologic involvement of the lymph nodes in both inguinal regions. Lymph node fine needle aspiration of lymph nodes in the left and right inguinal area revealed pleomorphic infiltrate of lymphoid cells with hemosiderin or melanoma pigment in the cytoplasm, so the lymph node biopsy with histopathological analysis was recommended. Multi-slice computer tomography (MSCT) examination of the head, chest, abdomen and pelvis revealed the absence of distant metastases. Cytoscopy revealed edema and partial pigmentation of the urethra adjacent to the external meatus, with no other pathologic findings.

Multidisciplinary tumor board consisting of urologist, consultant gynaecologist, dermatologist, plastic and reconstructive surgeon and pathologist indicated wide excision of melanoma with 1 cm margins, resection of the urethra and reconstruction, as well as left inguinal lymph node biopsy. Surgery was performed by urologist specialized in gender



**Figure 3 a and b.** Histopathological analysis revealed lentiginous spread of melanocytes showing moderate atypia, with focal pagetoid spread, no mitoses and ulceration, without invasion of lamina propria, and intensive inflammatory infiltrate present in lamina propria



**Figure 4.** Local finding two months after surgery, during follow-up

transformation and plastic and reconstructive surgeon.

Histopathological analysis revealed lentiginous spread of melanocytes showing moderate atypia, with focal pagetoid spread, no mitoses and ulceration, without invasion of lamina propria, and intensive inflammatory infiltrate present in lamina propria (**Figure 3a and 3b**). Resection margins were tumour-free, and histopathological analysis of lymph node biopsy revealed reactive lymphadenitis without pathological infiltration (0/4). Postoperative recovery was favourable, without intraoperative or postoperative complications. Multidisciplinary tumor board indicated regular follow-up. During the follow-up no signs of recurrence were noted (**Figure 4**). The last follow-up was in April 2019, without signs of local recurrence. The patient complained of urinary incontinence, and was treated by urologist with solifenacin 5 mg/day.

## Discussion

Genital pigmented lesions can be found in up to 10-12% of the general population [12]. Vulvar cancer is a rare neoplasm, accounting for less than 1% of malignant neoplasms among women. It represents 3-5% of malignant neoplasms of the female genital organs and has an estimated incidence of 1-2 cases per 100,000 women/year among women diagnosed with vulvar cancer in the United States (11). A vast majority (80%) of vulvar cancers are squamous cell carcinomas (SCC), whereas basal cell carcinomas (BCCs) and melanomas are less common, representing 8 and 6% of all vulvar cancers respectively (13). Sarco-

ma, basal cell carcinoma, and vulvar Paget's disease account for less than 2% of cases (14). The labia major is the most commonly affected site (52%) followed by the labia minor (18%), clitoris (10-15%) and Bartholin's glands (1-3%) (15). Postmenopausal women have a higher incidence of vulvar melanoma than premenopausal women, as was the case with our patient (12). Vulvar melanoma is a rare disease with different histological types. The order of incidence is as follows: mucosal lentiginous (27-57%), nodular (22-28%), unclassified (12-16%), and superficial spreading (4-56%) (16, 17). Risk factors include chronic inflammation, such as those associated with lichen sclerosis (18).

Differential diagnosis includes the following lesions: benign pigment lesions (lentigo simplex, vulvar melanosis, acanthosis nigricans, seborrheic keratosis, intradermal, junction or complex nevus), pigmented vulvar intraepithelial neoplasia, vulvar squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and Paget's disease (10).

In dermoscopy, the combination of blue, grey, or white colour with structureless zones are the strongest indicators of vulvar melanoma when differentiating between benign and malignant mucosal lesions as Blum et al. described [11]. Furthermore, polymorphous vessels are also a hint for malignancy, particularly melanoma (19, 20).

Early signs of a melanoma of the mucosa can include the presence of structureless parts and grey colour. Additional late-stage signs in larger lesions can include the presence of multiple patterns and additional colours, especially blue or white. However, the results of study conducted by Blum et al. show that multiple colours are a better clue to malignant lesions than multiple patterns (11).

In early stages there are no associated symptoms, and without regular gynaecological follow-up, intramucosal melanoma can progress to invasive vulvovaginal mucosal melanoma that becomes symptomatic. Pruritus, vaginal bleeding or discharge, dyspareunia or palpable mass are often present (10). Our patient had mild occasional pruritus and subjective feeling of difficulty in urinating, due to the urinary meatus infiltration and oedema, with no other symptoms.

Complete excision of the lesion is indicated in cases with suspected diagnosis. Currently, surgery still remains the best option albeit with-

out the need for radical procedures. A number of studies have shown that radical surgery does not increase the patient's survival with initial disease compared to local excision with margins, and is associated with greater morbidity and anatomical disfiguring (1, 13). Consequently, radical vulvectomy with bilateral lymphadenectomy is becoming a questionable and obsolete treatment approach. Alternatively, wide local excision with a 1 cm surgical margin is recommended for lesions with a depth of less than 1 mm. For deeper lesions en bloc resection with a safety margin of 2-3 cm and regional lymphadenectomy (inguinal-femoral) is advised. Adjuvant treatment with immunotherapy, chemotherapy, and radiotherapy may be recommended in specific cases and for local recurrences and distal metastases (13, 19, 20); however, it was not the case with our patient.

### Conclusion

The accurate and prompt diagnosis is essential in the case of vulvar melanoma. Generally, it has an unfavorable and relatively unpredictable prognosis, tending to recur and form metastases. Surgical treatment is the cornerstone of the therapeutic management. The initial surgical intervention must be optimally chosen in order to prevent the recurrence. The size of the tumor, the thickness and invasion degree, as well as ulceration and involvement of lymph nodes (LN), the patient's age at the time of diagnosis are essential factors influencing the survival. Women in postmenopausal age tend to have slightly higher incidence of vulvar melanoma than premenopausal women. Some studies have shown that the general prognosis of patients with vulvar melanoma is worse than the one in women with extra genital melanoma and squamous cell carcinoma of the vulva, showing a greater tendency for local and distal recurrence. In order not to miss an opportunity for early detection of mucosal melanoma, dermatologists and gynecologists should not avoid biopsy of lesions that demonstrate any clinical or dermoscopic features of melanoma, especially in older patients. Larger studies are needed to define more rigorously clinical and dermoscopic criteria that accurately distinguish early mucosal melanomas from benign skin lesions.

### Abbreviations

PH – B-45 - Human Melanoma Black - 45  
 IHH – Immunohistochemistry  
 LN – lymph nodes  
 MRI – Magnetic Resonance Imaging  
 LDH – Lactate Dehydrogenase  
 TSH – thyroid-stimulating hormone  
 CEA – Carcinoembryonic antigen

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## Rekurentni melanom vulve – prikaz slučaja

### Sažetak

Melanomi genitalnog područja, a naročito melanomi vulve su retki. Melanom vulve čini 5% svih maligniteta vulve i češće se javljaju kod žena u postmenopauzi. Glavna diferencijalna dijagnoza su vulvarna melanoza i nevusi vulve. Postoji mali broj studija o dermoskopskim karakteristikama melanoma sluzokože, a naročito lezija u ranom stadijumu. Opisani su dermoskopski kriterijumi za dijagnozu melanoze vulve, a sprovedena su i ispitivanja koja su definisala dermoskopske karakteristike nevusa i melanoma vulve.

Predstavljamo slučaj 69-godišnje žene sa sumnjom na recidiv vulvarnog melanoma koja je ranije imala operaciju mukoznog lentiginoznog melanoma na malim usnama juna 2017. godine. Pet meseci nakon resekcije primarnog melanoma, pacijentkinja je primetila novu pigmentaciju na levoj i desnoj maloj usni kao i na otvoru uretre. Na kliničkom pregledu, evidentirana je nepravilna svetlosmeđa pigmentacija nejasnih granica na malim usnama i oko spoljnog otvora uretre. Dermoskopski nalaz ukazao je na melanocitnu leziju sa nejasno ograničenom iregularnom pigmentnom mrežom, bela i ružičasta polja bez strukture. Biopsijom sluznice vulve otkriven je melanom in situ, potvrđujući lokalni recidiv. Pretragom grudnog koša, abdomena i karlicekomputerizovanom tomografijom i ginekološkim pregledom nisu otkriveni sekundarni depoziti. Ultrazvukom regionalnih ingvinalnih limfnih čvorova otkriveni su uvećani limfni čvorovi u levom ingvinumu sa sumnjom na

patološko zahvatanje. Citološka analiza levog i desnog ingvinalnog limfnog čvora i cistoskopski nalazi bili su u granicama normale. Multidisciplinarni konzilijum za melanom indikovao je široku eksciziju sa marginama od 1 cm uz resekciju uretre i biopsiju sumnjivog limfnog čvora u levom ingvinumu. Histopatološkom analizom reseciranog dela sluzokože otkriveno je lentiginozno i pedžetoidno širenje melanocita koji pokazuju umerenu atipiju, bez mitozna i ulceracija i bez invazije lamine proprije (melanoma in situ), uz slobodne margine resekcije. Histopatološki nalaz biopsije limfnog čvora ukazao je na nespecifičnu inflamaciju, bez patoloških depozita melanoma. Tokom redovnih kontrola nije zabeležen recidiv bolesti.

Tačna i brza dijagnoza neophodna je u slučaju melanoma vulve, koji ima nepovoljnu i nepredvidivu prognozu, sa tendencijom lokalnih recidiva i regionalnih i udaljenih metastaza u slučaju invazivnog melanoma. Za sve pigmentne lezije vulve kod kojih postoji klinička i dermoskopska sumnja (razvoj iregularne pigmentacije koja se vremenom širi i menja, pojava solitarne amelanotične papule ili nodusa) neophodna je eksciziona ili u slučaju lezija velikog dijametara inciziona biopsija sa mesta sa dermoskopski iregularnim karakteristikama, naročito kod starijih pacijentkinja. Potrebne su veće studije da se jasnije definišu klinički i dermoskopski kriterijumi koji precizno razlikuju rane melanome sluznice od benignih lezija.

**Ključne reči:** Neoplazme vulve; Melanom; Dermoskopija; Dijagnoza; Lokalne rekurentne neoplazme; Prikazi slučajeva

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## FORTHCOMING EVENTS

### Dermatology and Venereology Events 2019

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
17-19 January, 2019	7th EADO School of Dermato-Oncology, Berlin, Germany		<a href="http://www.eado.org">www.eado.org</a>
27-30 March, 2019	4th Dermatology and Cosmetology Congress with International Participants (NDERCOS 2019), Istanbul, Turkey	27 January, 2019	<a href="http://www.indercos.org">www.indercos.org</a>
24-27 April, 2019	15th EADO Congress of Dermato-Oncology, Paris, France		<a href="http://www.eadoparis2019.com">www.eadoparis2019.com</a>
10-15 June, 2019	24th World Congress of Dermatology, Milan, Italy	15 September, 2018	<a href="http://www.wcd2019milan.org">www.wcd2019milan.org</a>
9-13 October, 2019	28th EADV Congress, Madrid, Spain		<a href="http://www.eadv.org">www.eadv.org</a>
28 November - 1 December, 2019	3th National Medical Aesthetics Congress, Antalya, Turkey	25 September, 2019	<a href="http://www.mastder2019.org">www.mastder2019.org</a>

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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.

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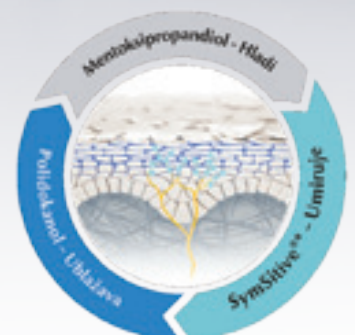
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