

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 homosexual ($p = 0.026$). 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 (%)	<i>p</i> 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
Sexualorientation				
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 necklace 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

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 palmo-plantar 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



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



Figure 7. Mucous patch in the oral cavity

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).

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.

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Abbreviations

HIV – human immunodeficiency 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 dijagnostikovao 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