



The Brazilian Journal of INFECTIOUS DISEASES

www.elsevier.com/locate/bjid



Case report

Secondary syphilis in the oral cavity and the role of the dental surgeon in STD prevention, diagnosis and treatment: a case series study

Creta Elisa Seibt^a, Maria Cristina Munerato^{a,b,*}

^a Universidade Federal do Rio Grande do Sul (UFRGS), Faculdade de Odontologia, Porto Alegre, RS, Brazil

^b Universidade Federal do Rio Grande do Sul (UFRGS), Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

ARTICLE INFO

Article history:

Received 23 December 2015

Accepted 20 March 2016

Available online 18 May 2016

Keywords:

Oral manifestations

Secondary syphilis

Treponema pallidum

ABSTRACT

Syphilis is an infectious disease caused by the bacterium *Treponema pallidum*. Syphilis has three clinical stages and may present various oral manifestations, mainly at the secondary stage. The disease mimics other more common oral mucosa lesions, going undiagnosed and with no proper treatment. Despite the advancements in medicine toward prevention, diagnosis, and treatment syphilis remains a public health problem worldwide. In this sense, dental surgeons should be able to identify the most common manifestations of the disease in the oral cavity, pointing to the role of this professional in prevention and diagnosis. This study describes a case series of seven patients with secondary syphilis presenting different oral manifestations.

© 2016 Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Humans are the only natural host known to date of syphilis, an infectious disease caused by the bacterium *Treponema pallidum*. This microorganism has positive tropism for several human organs and tissues, with complex clinical implications. Transmission occurs mainly through unprotected sexual intercourse and although the main inoculation site is the genital organs in general, extragenital areas such as the oral cavity and the anal region are also affected.^{1–5} Other important transmission pathways include the intra-uterus (transplacental) route during labor,^{1,4} which causes congenital syphilis.

Syphilis has three clinical stages. The primary stage is characterized by a single chancre that manifests approximately 90

days after exposure and remits spontaneously within two to eight weeks. The secondary stage occurs between 2 and 12 weeks after exposure, when a rash develops on several parts of the skin. The rash subsides spontaneously with no treatment when the condition enters its latent stage. Also called late phase and rarely observed today, the tertiary stage is characterized by gummata and/or neurosyphilis that emerge three years or later after exposure.^{1,3–10}

Although oral manifestations of syphilis may be observed at the primary stage, they are more commonly detected at the secondary stage of the disease as multiple painless aphthous ulcers or irregularly shaped lesions with whitish edges distributed on the oral mucosa and oropharynx, especially on the tongue, lips, and jugal mucosa.^{4,6,9} The appearance of such lesions varies widely, thus increasing the diagnostic

* Corresponding author.

E-mail address: mcmunerato@gmail.com (M.C. Munerato).

<http://dx.doi.org/10.1016/j.bjid.2016.03.008>

1413-8670/© 2016 Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1 – Oral anatomical sites affected, type of fundamental lesion and differential diagnosis.

	Oral anatomical site(s) affected	Fundamental lesion	Differential diagnosis
Patient 1 Male 45 years old Married	A – Upper lip mucosa near the commissure C – Tongue edge B – Lip commissure	Ulcer and mucous plaque Nodule and ulcer Nodule and ulcer	Lichen planus, pemphigus vulgaris Ulcer by trauma Angular cheilitis
Patient 2 Male 46 years old Single	C – Hard palate A – Lower lip mucosa B – Ventral tongue	Ulcer Mucous plaque Mucous plaque	Spinocellular carcinoma Apthous ulcer Apthous ulcer
Patient 3 Male 42 years old Single	A/B – Bilateral tongue edge	Nodule	Trauma by biting, fibroepithelial hyperplasia
Patient 4 Female 53 years old Married	A/B – Soft palate, involving tonsil pillars	Nodule and ulcer	Spinocellular carcinoma (simultaneous)
Patient 5 Female 29 years old Long term relationship	A – Soft palate A – Hard palate B – Lower lip mucosa	Mucous plaque Mucous plaque Spot and erosion	Ulcer by trauma Ulcer by trauma Leukoplakia, lichen planus
Patient 6 Female 39 years old Married	A/B – Apex and edge of tongue, bilaterally	Mucous plaque	Pseudomembranous candidiasis, lichen planus, pemphigus vulgaris
Patient 7 Female 36 years old Long term relationship	A – Uvula and palate tonsil	Mucous plaque	Ulcer by trauma, spinocellular carcinoma

complexity when the dental surgeon is not properly qualified to detect stomatological conditions. For this reason, oral manifestations of syphilis may be mistaken for other, more common oral conditions, with no early diagnosis or appropriate treatment.

In addition to information obtained directly from the patient during consultation, the diagnosis of syphilis normally includes clinical examination and serological and microbiological assays. As a rule, biopsy is only required when lesions do not subside completely. Standard laboratory assays used to diagnose syphilis at any stage include treponemal and non-treponemal serum tests.^{3,9}

Based on penicillin, the first successful anti-syphilis treatment was documented in 1943. Since then, penicillin is the drug of choice to treat the disease, usually penicillin G benzathine or penicillin G procaine.^{1,6}

This case series describes different oral manifestations of secondary syphilis in seven heterosexual patients. The objective was to discuss the diagnosis and treatment protocols adopted by the Stomatology Unit, Hospital de Clínicas de Porto Alegre (HCPA), Rio Grande do Sul, Brazil and to characterize secondary syphilis lesions in the oral cavity and the respective clinical follow-up of patients toward cure.

Clinical cases series

Herein we present seven patients with oral manifestations of secondary syphilis that were referred to our Stomatology Unit.

Table 1 shows the demographic data of the patients including age group, gender, and marital status.

All patients were initially seen at primary healthcare centers complaining of multiple painful lesions in the mouth as their main health problem, and went through the same medical diagnostic protocol (Fig. 1). HIV and hepatitis C exams requested were negative for all patients, and none admitted drug addiction. The most common fundamental lesions were plaques on the mucosa, ulcers, nodules, spots, and erosion, in this order. The most affected anatomical sites included labial mucosa, tongue edge, hard and soft palates, lip commissure, ventral tongue, uvula, and tonsils, respectively. Fig. 2 shows photographs of the oral lesions of each patient. The most frequent diseases considered in the differential diagnosis were ulcers caused by trauma, spinocellular carcinoma, and autoimmune diseases. Table 1 lists the oral sites affected, the fundamental lesion type, and the differential diagnosis for each lesion.

The venereal disease research laboratory (VDRL) test and the fluorescent treponemal antibody absorption (FTA-ABS) test were carried out for all patients, which are conventionally requested to diagnose syphilis. Results of both tests are shown in Fig. 3,¹¹ while serological assay results are shown in Table 2.

Upon confirmation of the diagnosis of syphilis, all patients received the conventional treatment as described by Brazilian health authorities.¹² This treatment includes intramuscular injections of penicillin G benzathine 2,400,000 IU a week for three weeks, and follow-up with serological assays until VDRL

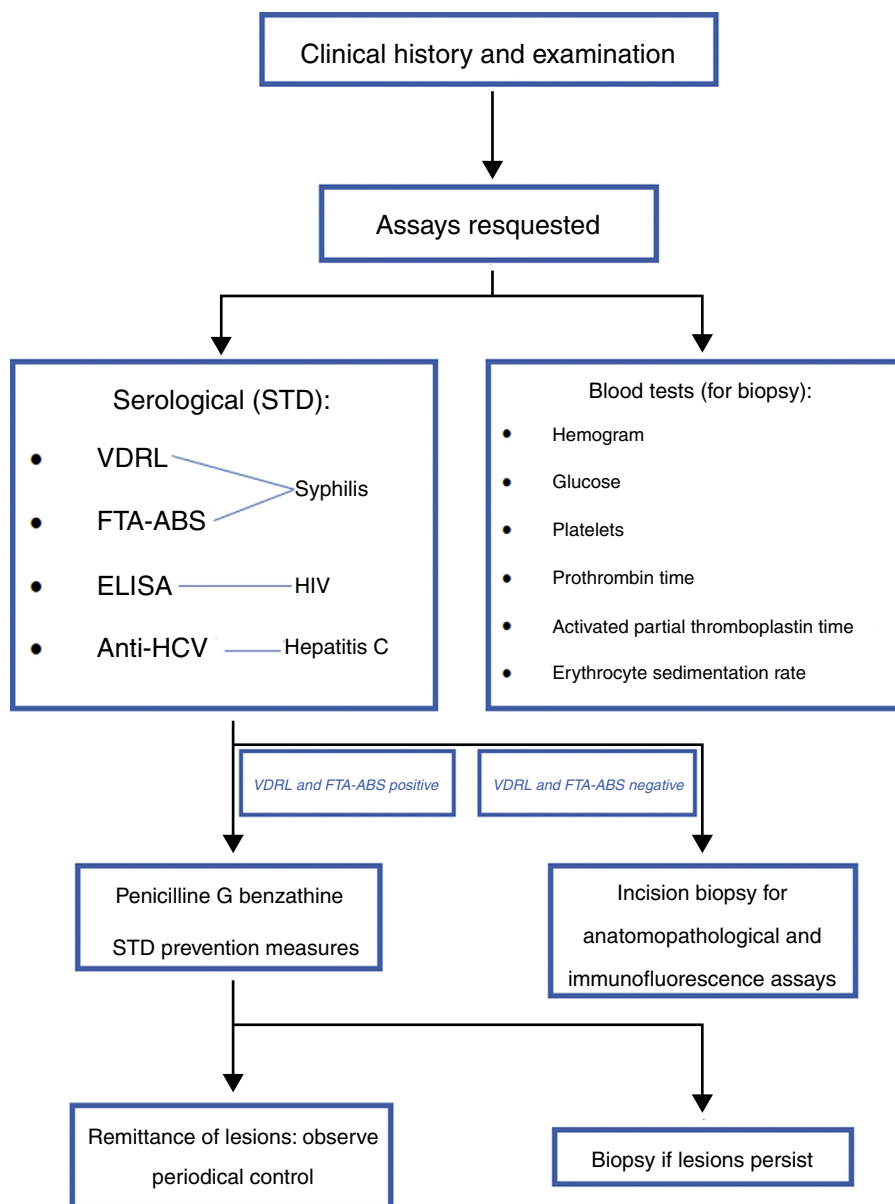


Fig. 1 – Protocol to diagnose and treat syphilis.

Table 2 – Results of serological assays. Assays were conducted at approximately 30-day intervals.					
	1st assay	2nd assay	3rd assay	4th assay	5th assay
Patient 1	VDRL – positive 1:1024 FTA ABS – positive	VDRL – positive 1:32 FTA ABS – positive	VDRL – positive 1:2 FTA ABS – positive		
Patient 2	VDRL – positive 1:128 FTA ABS – positive	VDRL – positive 1:32 FTA ABS – positive	VDRL – positive 1:4 FTA ABS – positive	VDRL – positive 1:2 FTA ABS – positive	VDRL – positive 1:1 FTA ABS – positive
Patient 3	VDRL – positive 1:32 FTA ABS – positive	VDRL – positive 1:2 FTA ABS – positive			
Patient 4	VDRL – positive 1:128 FTA ABS – positive	VDRL – positive 1:64 FTA ABS – positive	VDRL – positive 1:16 FTA ABS – positive	VDRL – positive 1:8 FTA ABS – positive	VDRL – positive 1:2 FTA ABS – positive
Patient 5	VDRL – positive 1:32 FTA ABS – positive	VDRL – positive 1:1 FTA ABS – positive			
Patient 6	VDRL – positive 1:128 FTA ABS – positive	VDRL – positive 1:32 FTA ABS – positive	VDRL – positive 1:4 FTA ABS – positive	VDRL – positive 1:2 FTA ABS – positive	VDRL – positive 1:2 FTA ABS – positive
Patient 7	VDRL – positive 1:16 FTA ABS – positive	VDRL – positive 1:2 FTA ABS – positive			

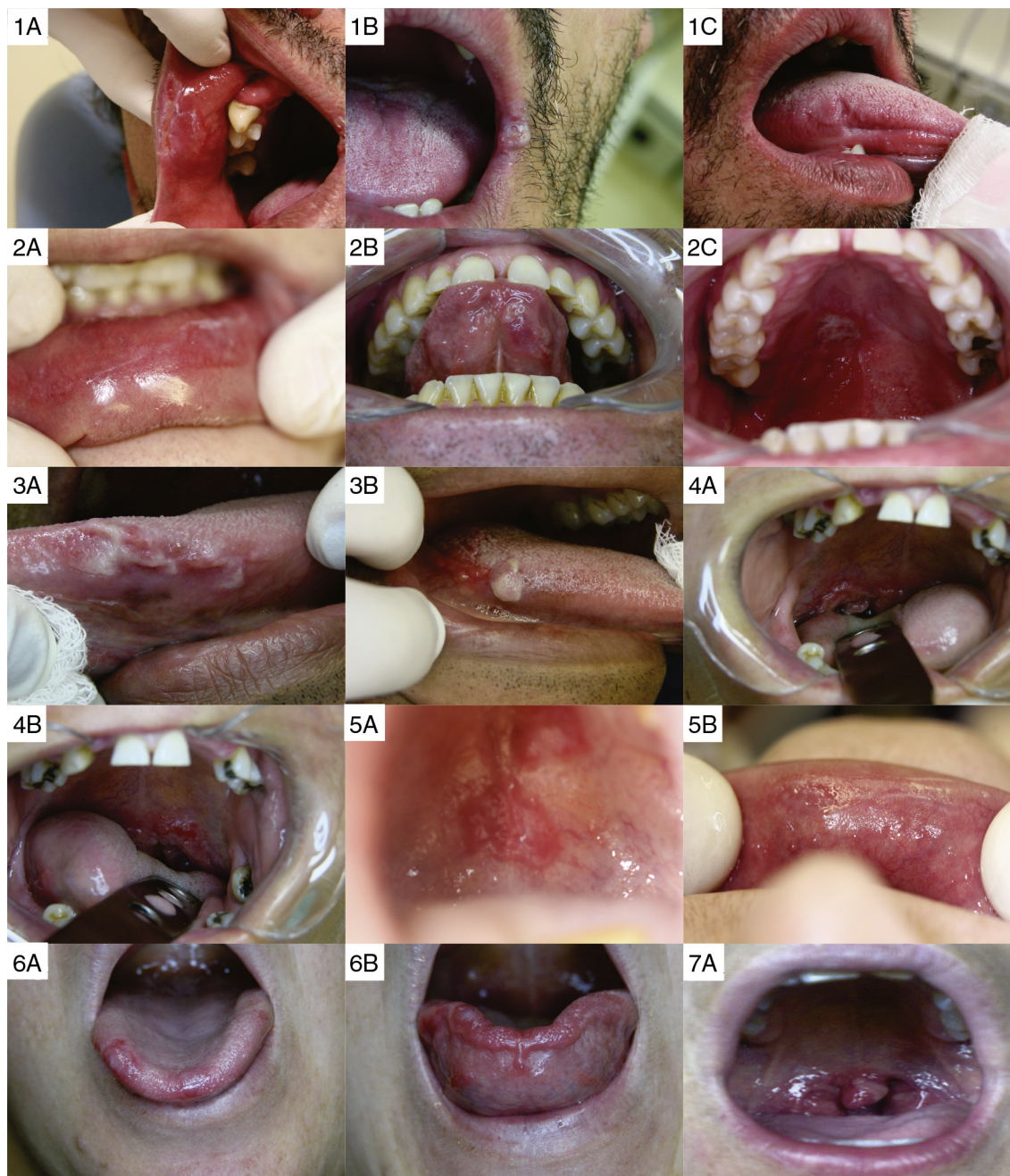


Fig. 2 – Photographs of the oral lesions of each patient.

titer levels are reduced. Patients are also instructed as to the importance of safe sexual practices, the risk of reinfection when sexual partners are not treated for the disease, and the risk of acquiring HIV and other STDs.

Oral manifestations of secondary syphilis disappeared completely within one to two weeks after the first penicillin injection avoiding the need to carry out biopsy.

Discussion

STDs are among the main public health problems, causing increasing concern worldwide.¹³ Approximately 12,000,000

new cases worldwide are estimated to occur every year.¹⁴ Syphilis stands out as an important epidemiological marker in the investigation of other STDs, mainly HIV infection.¹⁵ In Brazil, an estimated 900,000 new cases are diagnosed every year.¹⁶

Two types of syphilis have been described. Congenital syphilis is vertically transmitted, while the acquired form of the disease is an STD.^{3,4} Acquired syphilis has three clearly distinct clinical stages, called primary, secondary, and tertiary. In addition, the literature mentions a latent stage, which comprises the timespan following infection with *T. pallidum*, characterized by sero-reactivity and no other evidence of the disease.^{1,4,5,7,8} All patients whose records were analyzed in the

Interpretation of VDRL and FTA-ABS assays	
•	VDRL positive and FTA-ABS positive: active or latent syphilis de sífilis ativa ou sífilis latente
•	VDRL positive and FTA-ABS negative: other disease
•	VDRL negative and FTA-ABS positive: primary or treated syphilis
•	VDRL negative and FTA-ABS negative: syphilis if ruled out
Note: FTA-ABS result will remain positive for life, even when the patient is cured.	
Source: Brazilian Health Ministry, 2010	

Fig. 3 – Interpretation of VDRL and FTA-ABS assays.

present study had been diagnosed with secondary syphilis, which is characterized by muco-cutaneous manifestations and by hematogenous dissemination that elicits the colonization of several organs.^{1,17} This stage starts within three to five months after infection. However, if not treated, secondary syphilis may recur as late as two years after exposure.¹⁸ It is accompanied by unspecific clinical signs and symptoms, such as general discomfort, headache, low-grade fever, anorexia, weight loss, and lymphadenopathy.^{4,9,17,18} Pharyngitis, myalgia, and arthralgia may also be present.⁹ These conditions disappear spontaneously, with no treatment, during the latent period.^{1,4,5,7,9}

Oral manifestations of secondary syphilis include multiple, scattered lesions on the oral mucosa and oropharynx, though the tongue, lips, and jugal mucosa are the most commonly affected sites. Aphthous ulcers similar to gray plaques or ulcers with irregular, whitish edges that are painful at times are also observed. The diffuse character of the inflammatory process in the oropharynx may elicit complaints of sore throat.^{4,6,9} Oral lesions varies widely in appearance, increasing the complexity of diagnosis if the dental surgeon lack the required qualifications in stomatology. In contrast to primary syphilis, secondary syphilis in the oral cavity is not associated with oral sex habits.

The patients analyzed in the present study exhibited multiple lesions in the oral cavity caused by syphilis with the exception of patient 7, who exhibited a lesion in the uvula only. The lip mucosa and the tongue edge were the anatomical sites most frequently affected (in four patients each), followed by the hard and soft palates (in two patients each), ventral tongue, lip commissure, uvula, and tonsils (in one patient each). The fundamental lesions most commonly detected were mucous plaque (in seven anatomical sites), ulcer (in five), nodule (in four), spot and erosion (in one site each) (Table 1).

Clinical history, physical examination, and serological and microbiological assays are usually sufficient to diagnose syphilis. The information obtained in the present case series show that serological assays for syphilis should be requested from all suspected patients as a means to reach differential diagnosis. Therefore, depending on the clinical manifestation, differential diagnosis are trauma caused by bites, fibroepithelial hyperplasia, lichen planus, pemphigus vulgaris, ulcer associated with trauma, angular cheilitis, spinocellular carcinoma, aphthous ulcers, and leukoplakia (Table 1). The variety

of differential diagnosis in this case series confirms the findings described in previous studies, that is, secondary syphilis takes on several manifestations in the oral cavity, in which case the disease mimics other more frequent lesions in the oral mucosa, occasionally proceeding along its course with no proper diagnosis and treatment.^{1–4,8,9}

The serology assays requested for the patients in the present study included VDRL and FTA-ABS to investigate syphilis, and enzyme-linked immunosorbent assay (ELISA) for HIV and HCV. All patients had positive VDRL and FTA-ABS results (Table 2), confirming the diagnosis of secondary syphilis. The results of HIV and HCV tests were all negative.

It has been shown that patients with syphilis are at higher risk of acquiring other STDs, especially HIV infection, since the syphilitic lesions are suitable sites for the virus to enter the human body.⁶ This highlights the importance of instructing patients as to preventive measures concerning safe sexual behavior, appropriate medical treatment of partners diagnosed positive for any relevant disease, and the awareness of the risks around sharing needles.

Treponemal and non-treponemal assays are the standard laboratory tests used to detect the presence of syphilis at any stage.^{3,9} Results of positive non-treponemal assays are reported as the lowest positive dilution. These assays are suitable for evaluating response to treatment and to assess the likelihood of reinfection. However, these tests are not indicated during the latent stage of the disease due to their poor sensitivity.¹⁸ These assays include the VDRL and its simplified version, the rapid plasma regain (RPR) test.^{3,9} Due to their increased specificity and sensitivity, the treponemal assays *Treponema pallidum* particle agglutination assay (TPPA), the FTA-ABS assay, and ELISA are used mainly as diagnosis confirmation tools.^{3,9} However, these tests do not clarify activity of the disease and, in most cases, will always remain positive, even after successful treatment.¹⁸

In a systematic review and meta-analysis, the sensitivity and specificity of fast treponemal assays were shown to be comparable to those of standard methods.¹⁹ The authors concluded that when resources are limited (that is, when access to laboratories is difficult and screening for syphilis is not conducted), the fast detection assays are useful alternatives.

The first effort to treat syphilis was successfully conducted in 1943, using penicillin, which has since retained its status as drug of choice for treating of all stages of syphilis. Both penicillin G benzathine or penicillin G procaine are used for this purpose.^{1,6} The Brazilian Ministry of Health defines a single 2,400,000 IU intramuscular dose of penicillin G benzathine as the treatment of choice for both primary and secondary syphilis. However, the tertiary stage of the disease is treated with the same dose, repeated weekly for three weeks.^{5,12} Due to the difficulty to determine whether secondary syphilis in the cases evaluated was at the early or late stages, the treatment for late secondary syphilis was adopted in order to improve the chances of success.

For patients hypersensitive to penicillin, oral administration of doxycycline 100 mg twice a day for 14 days or tetracycline 500 mg four times a day for 14 days is indicated, with similar efficacy. These regimens are effective to treat primary, latent secondary, and early secondary stages of syphilis. Cases estimated to be in progress for one year or more (or

when it is not possible to establish date of infection), treatment duration is increased to 28 days, either with doxycycline or tetracycline.^{1,5}

Evidence indicates that azithromycin 1 g a week for two to three weeks is effective to treat syphilis in penicillin-hypersensitive patients. However, the specialized literature warns that resistance to azithromycin has emerged quickly.⁹

Although the treatment protocols for syphilis have been clearly defined, few randomized clinical studies have been conducted to ascertain whether azithromycin or penicillin G are more effective to treat early syphilis. For each individual case, the decision to prescribe one or other of these drugs should be based on an evaluation of the cost-benefit relationship and on any risks the patient may have to face.³ A systematic review has recommended that azithromycin should be prescribed to treat early syphilis, though it has to be considered an alternative approach when the patient has hypersensitivity to penicillin or doxycycline is not a feasible option.²⁰ The records of all patients analyzed in the present study show that none had such hypersensitivity.

Conclusion

In spite of the advances in medicine toward the prevention and early diagnosis and treatment of syphilis, the disease remains a public health problem worldwide. The growing prevalence of the disease in immunocompetent individuals is reason for concern, indicating poor compliance with safe sex practices to prevent STDs. Primary syphilis may be observed in the oral cavity, and has been associated with oral sex. The secondary stage of the disease takes a variety of oral manifestations, mimicking other more frequent lesions in the oral cavity, going by undetected and hence remaining without proper treatment. The analysis of a suspected patient's clinical history, combined with physical examination and serological assays normally affords a conclusive diagnosis of the disease, and biopsy is not normally required as an initial diagnostic resource. Therefore, the dental surgeon should be aware of the most common manifestations of syphilis in the oral mucosa so as to play a role not only in the treatment of syphilis, but also in the diagnosis of the disease.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Ficarra G, Carlos R. Syphilis: the renaissance of an old disease with oral implications. *Head Neck Pathol.* 2009;3:195-206.
2. Ikenberg K, Springer E, Wolfgang B, et al. Oropharyngeal lesions and cervical lymphadenopathy: syphilis is a differential diagnosis that is still relevant. *J Clin Pathol.* 2010;63:731-6.
3. Leuci S, Martina S, Adamo D, et al. Oral syphilis: a retrospective analysis of 12 cases and a review of the literature. *Oral Dis.* 2013;19:738-46.
4. Little JW. Syphilis: an update. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol.* 2005;100:3-9.
5. Viñals-iglesias H, Chimenos-küstner E. The reappearance of a forgotten disease in the oral cavity: syphilis. *Med Oral Patol Oral Cir Bucal.* 2009;14:416-20.
6. Angus J, Langan SM, Stanway A, Leach IH, Littlewood SM, English JS. The many faces of secondary syphilis: a re-emergence of an old disease. *Clin Exp Dermatol.* 2006;31:741-5.
7. Baughn RE, Musher DM. Secondary syphilitic lesions. *Clin Microbiol Rev.* 2005;18:205-16.
8. Compilato D, Amato S, Campisi G. Resurgence of syphilis: a diagnosis based on unusual oral mucosa lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol.* 2009;108:e45-9.
9. Noronha ACC, Israel MS, Almeida DCF, Moreira GM, Lourenço SQC, Dias EP. Sífilis secundária: diagnóstico a partir das lesões orais. *DST - J Bras Doenças Sex Transm.* 2006;18:190-3.
10. Ramoni S, Cusini M, Crosti FGC. Syphilitic chancres of the mouth: three cases. *Acta Derm Venereol.* 2009;89:648-9.
11. Sífilis: estratégias para diagnóstico no Brasil. Brasília: Ministério da Saúde, Coordenação de Doenças Sexualmente Transmissíveis e Aids. 2010. 100 p. (Série TELELAB). Access to: <http://www.aids.gov.br/sites/default/files/anexos/page/2012/50768/manual.sifilis.miolo.pdf.53444.pdf>.
12. Secretaria de Vigilância em Saúde. Programa Nacional de DST e Aids. Protocolo para a prevenção de transmissão vertical de HIV e sífilis: manual de bolso. Brasília, Brasil: Ministério da Saúde; 2007, 180 p.: il. - (Série B. Textos Básicos de Saúde).
13. Plano operacional para a redução da transmissão vertical do HIV e da sífilis no Brasil. Brasília, Brasil: Ministério da Saúde; 2007.
14. Organização Mundial da Saúde. Eliminação mundial da sífilis congênita: fundamento lógico e estratégia para ação. Genebra, Suíça: WHO Press; 2008.
15. Dia Nacional de Combate à Sífilis: governo e sociedade civil juntos rumo à eliminação até 2015. Brasil: Departamento de IST, Aids e Hepatites Virais; 2012. Available from: <http://www.aids.gov.br/noticia/2012/dia-nacional-de-combate-sifilis-governo-e-sociedade-civil-juntos-rumo-eliminacao-ate-20> [accessed 26.03.15].
16. Dia Mundial de Combate à Sífilis: OMS estima 900 mil casos/ano da doença. Brasil: Governo do Estado da Bahia; 2012. Available from: http://www.saude.ba.gov.br/index.php?option=com_content&view=article&id=4971:dia-mundial-de-combate-a-sifilis-oms-estima-900-mil-casosano-da-doenca-&catid=1:noticiascidadadaousuario&Itemid=14 [accessed 26.03.15].
17. Ho EL, Lukehart SA. Syphilis: using modern approaches to understand an old disease. *J Clin Invest.* 2011;121:4584-92.
18. Read PJ, Donovan B. Clinical aspects of adult syphilis. *Intern Med J.* 2012;42:614-20.
19. Jafari Y, Peeling RW, Shivkumar S, Claessens C, Joseph L, Pai NP. Are *Treponema pallidum* specific rapid and Point-of-Care tests for syphilis accurate enough for screening in resource limited setting? Evidence from a meta-analysis. *PLOS ONE.* 2013;8:e54695.
20. Ghanem KG, Workowski KA. Management of adult syphilis. *Clin Infect Dis.* 2011;53 Suppl. 3:S110-28.