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REVIEW ARTICLE

Oral Syphilis: a retrospective analysis of 12 cases and a review of the literature

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OBJECTIVE: To present a retrospective analysis of multicentre case series of oral syphilis and a review of relevant literature.

SUBJECTS AND METHODS: A PUBMED search was carried out from 1950 to 2011. Clinical records of patients with exclusive/prevalent oral manifestations of syphilis were collected and examined in three independent hospitals.

RESULTS: Of 23 reports describing 34 patients were detected through the review (35% primary, 56% secondary, and 9% tertiary disease), describing unspecific ulcers (59%), mucosal patches (23%), keratosis (6%), pseudomembranes (3%), and gumma (9%). Multicentre case series revealed 12 patients with oral syphilis, of which 17%, 58%, and 25% with, respectively, primary, secondary, and tertiary lesions. Clinically, patients showed white patches (17%), blistering mucositis (8%), chronic unspecific ulcers with/without skin lesions (50%), gumma (17%), and necrosis of the dorsum of the tongue (8%). Oral bullae and tongue necrosis are never described in the current review.

CONCLUSIONS: Diagnosis of syphilis remains a challenge because of the multiform and polymorphous clinical pattern at onset and its ability to imitate different diseases. It is mandatory to include syphilis in the differential diagnosis of unusual oral lesions. Diagnosis of oral lesions of syphilis is often difficult, and biopsy is required in controversial cases.

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Keywords: syphilis; treponema pallidum; oral mucosa

Introduction

Syphilis is a systemic sexually transmitted disease caused by the anaerobic spirochetes *Treponema pallidum,* which mainly affects humans and is able to invade practically any organ in the body. Without treatment, the infection of *Treponema Pallidum* often scanty of symptoms in the early stages, and can result in neurological, cardiovascular, and bone diseases later in life. Early syphilis in pregnant women can be associated with neonatal or latent infection in the child and fetal loss (WHO, 2001).

Being a very common disease for centuries, in 1940s, the introduction of penicillin therapy and campaigns of prevention made syphilis a rare disease (Kilmarx and St Louis, 1995), with a progressive decline of its prevalence and incidence (with 2.1 cases per 100 000 persons) in the US in the year 2000 (CDC, 2002). In the last few years, despite the introduction of established and standardized protocols of treatment, there has been a dramatic resurgence of this disease in several countries (Ficarra and Carlos, 2009). This changing epidemiology of syphilis reflects the decreasing use of barrier methods of contraception due to (i) a false sense of security deriving from the concept that sexually transmitted diseases are curable, (ii) high numbers of sexual partners, and sexual promiscuity, (iii) unprotected ano-genital and oral sex, (iv) to the growing activity of prostitution networks, and (v) the lack of pertinent knowledge among the general population (Ashton *et al*, 2003) (Koumans *et al*, 2001) (Poulton *et al*, 2001) (Okwumabua *et al*, 2001). The World Health Organization estimates that at least 12 million people are infected with syphilis in the world. Southeast Asia accounts for 5.8 million, while Africa accounts for 3.5 million (Bai *et al*, 2008).

The disease may also occur as a co-infection in HIV-seropositive patients. Syphilis can facilitate HIV transmission, and HIV can influence the clinical features and treatment outcomes of syphilis. About 50% to 60% of men who have sex with men (MSM) with early syphilis are HIV infected (Buchacz *et al*, 2005). In 2002, the CDC reported that 25% of primary and secondary syphilis cases occurred in persons co-infected with HIV, and the incidence rate of syphilis in HIV-infected persons was 77

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times greater than in the general population (Chesson *et al*, 2005). While the increasing incidence of syphilis may be due to high-risk behaviors, higher rates of syphilis and HIV co-infection may also be due to immunological and bacteriological factors. The primary chancre can facilitate acquisition and transmission of HIV by disrupting mucosal and epithelial barriers. In addition, the influx of immune cells to syphilis lesions increases the number of cellular targets available for HIV infection, and the proximity of HIV-infected cells to transmit virus to the partner (Ho and Lukehart, 2011). Because syphilis is a cofactor in HIV transmission, and HIV infection can enhance infection and modify clinical presentation of syphilis, high syphilis, and HIV co-infection rates within the sexual networks of MSM may enhance the spread of both sexually transmitted diseases (STDs) (Buchacz *et al*, 2005).

Transmission of syphilis occurs mostly through sexual intercourse. Even if the sites of inoculations are usually genital, they can also be extragenital (Alam *et al*, 2000). Although oral manifestations are rare, the importance of considering the diagnosis in the mouth has recently been highlighted in the primary, secondary, and tertiary stages (Sanchez, 1994).

Diagnosis of syphilis could be a challenge for clinicians, and oral health care providers must be aware of oral and systemic manifestations of syphilis at any stage, referring cases they diagnose to the reference centers for sexually transmitted diseases, where patients, especially with secondary or tertiary disease or with co-infections, are managed by a infectious disease specialists because of the development of systemic complications in the central nervous system and myocardium.

The aim of the study is to perform an update on the oral involvement of the disease through a review of the current literature. We also report a retrospective analysis of a multicentre case series of 12 patients in whom syphilis has presented in the oral cavity as the single or additional site of involvement.

Materials and methods

A PubMed search was carried out from 1950 to 2011 using the following keywords in multiple combinations: syphilis, oral syphilis, oral lesions, sexually transmitted diseases, systemic diseases. The selection of studies was based on the following inclusion criteria:

1 the English language;
2 a case series and case reports;
3 the availability of data on the detailed description of clinical manifestation of syphilis;
4 the availability of data on the diagnosis based on at least one immune pathological assay (hematoxylin and eosin, periodic acid-Schiff, Ziehl–Neelsen, or Warthin–Starry staining, or the streptavidin-biotinylated immunoperoxidase technique) and/or serological assay identifying the presence of *Treponema Pallidum* treponemal (fluorescent-treponemal-antibody absorption test, FTA-abs, or treponema pallidum hemagglutination assay, TPHA) or non-treponemal (Venereal Disease Research Laboratory/Rapid Plasma Reagin, VDRL/RPR)
5 the availability of data on HIV test

From our database, we retrospectively selected and analyzed the clinical data of syphilis patients in the outpatient clinic of the Department of Odontostomatological and Maxillo-Facial Sciences, Federico II University of Naples and the Department of Dental Sciences and Surgery, University of Bari, and Department of Clinical Specialistic and Stomatological Sciences, Polytechnic University of Marche, Ancona, Italy. The diagnosis was made through oral biopsy with immunohistochemical staining for *Treponema pallidum*, and at least one positive non-treponemal test (VDRL, IMMUTREP® VDRL ANTIGEN, United Kingdom) and one positive treponemal test (TPHA, KH1 test, Radim, Italy or FTA-abs, IgG kit, Alere, Italy) according to manufacturers' procedures. For VDRL, the results were visualized as reactive, weak reactive and non-reactive. For TPHA and FTA-abs tests, readings are scored by the degree of positivity/negativity and reported as 4+, 3+, 2+, 1+, +/− or negative.

Results

The analysis of literature revealed 23 reports of oral syphilis from 1950 to August 2011, which consisted of 34 patients, 28 males (82%) and six females (18%) (Table 1). The mean (±SD) age at the time of diagnosis of the disease was 41.5 (±11.3) for the males, and 24.8 (±12.1) for the females, ranging in age from 28 to 67 for the males and from 6 to 38 for the females. There were 12 cases of primary syphilis (35%), 19 of secondary syphilis (56%), and three cases of tertiary syphilis (9%).

Clinically, the primary lesions were mainly represented by ulcerated lesions (chancres) of which 7 (58%) were asymptomatic and 5 (42%) were painful. The chancre was localized on the tongue in 5 (42%) patients (Staines and Sloan, 2011; Flynn *et al*, 2010; Ramoni *et al*, 2009; Shumway *et al*, 2009), on the labial mucosa in 2 (17%) patients (Scott and Flint, 2005; Alam *et al*, 2000), on the commissure in 2 (17%) patients (Scott and Flint, 2005), on the buccal mucosa in 1 (8%) patient (Veraldi *et al*, 2008), on the palate in 1 (8%) patient, (Alam *et al*, 2000), and on the vestibular fornix in 1 (8%) patient (Ramoni *et al*, 2009).

The secondary lesions displayed a heterogeneous pattern: mucosal patches in 8 (42%) patients (Lu and Eng, 2002; Oztürk *et al*, 1998; Ban *et al*, 1995; Mani, 1984), solitary or multiple ulcerations in 7 (37%) patients (Rajlawat *et al*, 2011; Ikenberg *et al*, 2010; Murrell, 2009; Bruce *et al*, 2009; Lu and Eng, 2002; Ficarra *et al*, 1993), a leukoplakia-like plaque in 2 (11%) cases (Compilato *et al*, 2009; Aquilina *et al*, 2003), aphthous lesions in 1 (5%) case (Ibrahim and Malu, 2009), and pseudomembranous lesions in 1 (5%) case (Junkins-Hopkins, 1996).

In 5 (26%) cases, the oral lesions were multiples (Compilato *et al*, 2009; Lu and Eng, 2002; Junkins-Hopkins, 1996; Mani, 1984), while in the other 14 (74%) cases, the most frequent site of onset of the disease was the tongue (five cases, 37%) (Ikenberg *et al*, 2010; Bruce *et al*, 2009; Aquilina *et al*, 2003; Oztürk *et al*, 1998), followed by the labial (three cases, 21%) (Rajlawat *et al*,

Table 1 Description of clinical data of 34 patients from PUBMED search

References	*Gender*	*Age*	*Stage*	*Site*	*Type*	*Nontreponemal*	*Treponemal*	*Biopsy*	*Extragenital sites*	*Other diagnostic tests*	*Diagnosed by*	*Treatment*
Staines and Sloan (2011)	M	41	1	Tongue	Ulcer	+	n/a	1	n/a	Immunohistochemistry	Dentist	Penicillin
Rajlawat *et al* (2011)	M	39	2	Labial mucosa	Ulcer	+	+	1	Facial rash		Dentist	Penicillin
Ikenberg *et al* (2010)	M	47	2	Tongue	Ulcer	+	+	1	n/a	PCR, immunohistochemistry	Oral medicine	n/a
Ikenberg *et al* (2010)	M	67	2	Tongue	Ulcer	+	+	1	n/a	PCR, immunohistochemistry	Oral medicine	n/a
Flynn *et al* (2010)	M	37	1	Tongue	Ulcer	+	n/a	1	Erythema of the legs	TC of the neck	Maxillofacial surgeon	Doxycyclin
Ibrahim and Malu (2009)	F	24	2	Buccal mucosa	Aphtous ulcers	+	+	n/a	Rash of the palms	RMN (otosyphilis)	n/a	Doxycyclin
Compilato *et al* (2009)	M	45	2	Buccal mucosa, tongue	"Leukoplakia-like" plaque	+	+	1	None		Oral medicine	Erythromycin
Ramoni *et al* (2009)	M	28	1	Tongue	Ulcer	+	+	n/a	None		Dermatologist	Penicillin
Ramoni *et al* (2009)	M	37	1	Vestibular fornix	Ulcer	+	+	n/a	None		Dermatologist	n/a
Ramoni *et al* (2009)	M	45	1	Tongue	Ulcer	+	+	n/a	None		Dermatologist	n/a
Shumway *et al* (2009)	M	52	1	Tongue	Ulcers	+	+	n/a	None	PCR	Oral medicine	Penicillin
Murrell (2009)	M	58	2	Palate	Ulcer	+	+	n/a	n/a		Otorhinolaryngologist	Penicillin
Bruce *et al* (2009)	M	38	2	Tongue	Ulcer	+	n/a	1	Rash of trunk, palms and feet		Otorhinolaryngologist	Doxycyclin
Veraldi *et al* (2008)	M	31	1	Buccal mucosa	Ulcers	+	+	1	None		Dermatologist	Erythromycin
Scott and Flint (2005)	M	28	1	Labial mucosa	Ulcer	+	+	1	None		Oral medicine	Penicillin
Scott and Flint (2005)	M	36	1	Commissure	Ulcer	+	+	n/a	None		Oral medicine	Penicillin
Scott and Flint (2005)	F	24	1	Commissure	Ulcer	+	+	n/a	None		Oral medicine	Penicillin
Aquilina *et al* (2003)	M	41	2	Tongue	"Leukoplakia-like" plaque	+	+	1	None		n/a	Penicillin
Lu and Eng (2002)	M	58	2	Labial mucosa	Ulcers	+	+	1	Genital rash		n/a	Penicillin
Lu and Eng (2002)	M	30	2	Buccal mucosa	Mucous patches	+	+	1	Rash of the palms		n/a	Penicillin
Lu and Eng (2002)	F	38	2	Palate	Mucous patches	+	+	n/a	n/a		n/a	Penicillin
Lu and Eng (2002)	M	35	2	Palate, buccal mucosa	Mucous patches	+	+	n/a	n/a	Serologic tests for HIV	n/a	Penicillin
Alam *et al* (2000)	M	61	1	Labial mucosa	Ulcer	+	+	1	None		n/a	Penicillin
Alam *et al* (2000)	M	31	1	Palate	Ulcer	+	+	1	None	Immunohistochemistry	n/a	Penicillin
Oztürk *et al* (1998)	F	6	2	Tongue	Mucous patches	+	+	n/a	Genital lesions		Oral medicine	Penicillin
Junkins-Hopkins (1996)	F	38	2	Labial mucosa, tongue	Superficially ulcerated lesions with pseudomembranes	+	+	1	None		n/a	Penicillin
Ban *et al* (1995)	M	31	2	Hard palate	Mucous patches	+	+	1	n/a	Immunohistochemistry	Dermatologist	Penicillin
Ficarra *et al* (1993)	M	35	2	Gingiva	Multiple coalesced ulcerations	+	+	1	Rash of face, trunk and palms		Oral medicine	Penicillin
Mani (1984)	F	19	2	Labial and buccal mucosa	Mucous patches	+	n/a	n/a	n/a		Dentist	n/a
Mani (1984)	M	28	2	Labial mucosa	Mucous patches	+	n/a	n/a	n/a		Dentist	n/a
Mani (1984)	M	45	2	Labial mucosa, tongue	Mucous patches	+	n/a	n/a	Genital lesions		Dentist	n/a

(continued)

Table 1 (continued)

References	*Gender*	*Age*	*Stage*	*Site*	*Type*	*Nontreponemal*	*Treponemal*	*Biopsy*	*Extragenital sites*	*Other diagnostic tests*	*Diagnosed by*	*Treatment*
Ramstad and Traaholt (1980)	M	63	3	Palate	Cleft	n/a	+	1	Nasal ulceration		Dentist	Penicillin
Taylor and Hipple (1961)	M	43	3	Hard palate	Ulcerations	n/a		1	None		n/a	Penicillin
Huebsch (1955)	M	33	3	Hard palate	Sequestrum	n/a	n/a	1	None		n/a	n/a

n/a, not available; p, performed.
1 = primary syphilis.
2 = secondary syphilis.
3 = tertiary syphilis.

2011; Lu and Eng, 2002; Mani, 1984), the buccal mucosa (two cases, 14%) (Ibrahim and Malu, 2009; Lu and Eng, 2002), the palate (three cases, 21%) (Murrell, 2009; Lu and Eng, 2002; Ban *et al*, 1995), and the gingiva (1 case, 7%) (Ficarra *et al*,1993).

All tertiary lesions were gummas of which 2 (66%) (Taylor and Hipple, 1961; Huebsch, 1955) were on the hard palate and 1 (33%) (Ramstad and Traaholt, 1980) was on the soft palate creating a cleft.

The case series from our database revealed 12 patients with syphilis often with an unusual clinical aspect. The mean (±SD) age at the time of diagnosis of the disease was 55.7 (±15.8) for the males, and 35.3 (±11) for the females, ranging in age from 29 to 70 for the males and from 25 to 47 for the females. There were 1 (8%) case of primary syphilis, 8 (67%) of secondary syphilis, and 3 (25%) cases of tertiary syphilis. All 12 patients are HIV negative.

Case 1 – In 2008, a 29-year-old Caucasian man was referred to our oral medicine unit with a history of 4-week widespread lesions affecting the oral cavity. Physical examination showed: whitish and erythematous lesions of the lower labial mucosa and both commissures, and several mucous patches of the hard palate, the vestibular mucosa and the dorsum of tongue. He also had a symmetric maculopapular cutaneous rash of the palms, soles and trunk of the body (Figure 1a). Histopathology revealed an unspecific inflammatory infiltrate and VDRL, TPHA and FTA-abs tests were positive, allowing us to establish a diagnosis of secondary syphilis. The patient received 1 200 000 UI of benzylpenicillin benzatine (IM) twice a week, 6 weeks later, there were no lesions on oral and skin examination.

Case 2 – In 2009, a 47-year-old Caucasian women was referred to our unit with a desquamative gingivitis of the anterior lower teeth and a bullous-erosive lesion localized at the right edge of the tongue. The clinical, histopathological and immunological data were consistent with the diagnosis of pemphigus vulgaris. One week after commencing therapy, she developed circular papulo-squamous lesions of the palms and soles; therefore, we reconsidered the diagnosis suspecting a secondary syphilis, a diagnosis that was later confirmed. The clinical details have been previously described elsewhere (Mignogna *et al*, 2009).

Case 3 – In 2010, a 58-year-old Caucasian man was referred to our unit with a history of a 5-week asymptomatic ulcerated lesion of the palate. The patient was a smoker (about 40 cigarettes per day). Physical examination revealed an ulcer at the junction of the hard and soft palate, of 2 cm at its maximum diameter, with indurated margins, mimicking an oral cancer lesion. The histopathology showed an unspecific inflammatory infiltrate. Anamnesis revealed a history of syphilis 35 years, which had been previously treated with penicillin; the VDRL and TPHA tests were positive. Therefore, a reinfection with primary syphilis was diagnosed. The patient received 1 200 000 UI of benzylpenicillin benzatine twice a week, and the lesion healed after 4 weeks.

Case 4 – In 2011, a 63-year -old Caucasian man was referred to our unit with a history of a 4-week asymptomatic ulcer of the soft palate (Figure 1b). The patient was a smoker (about 20 cigarettes per day).

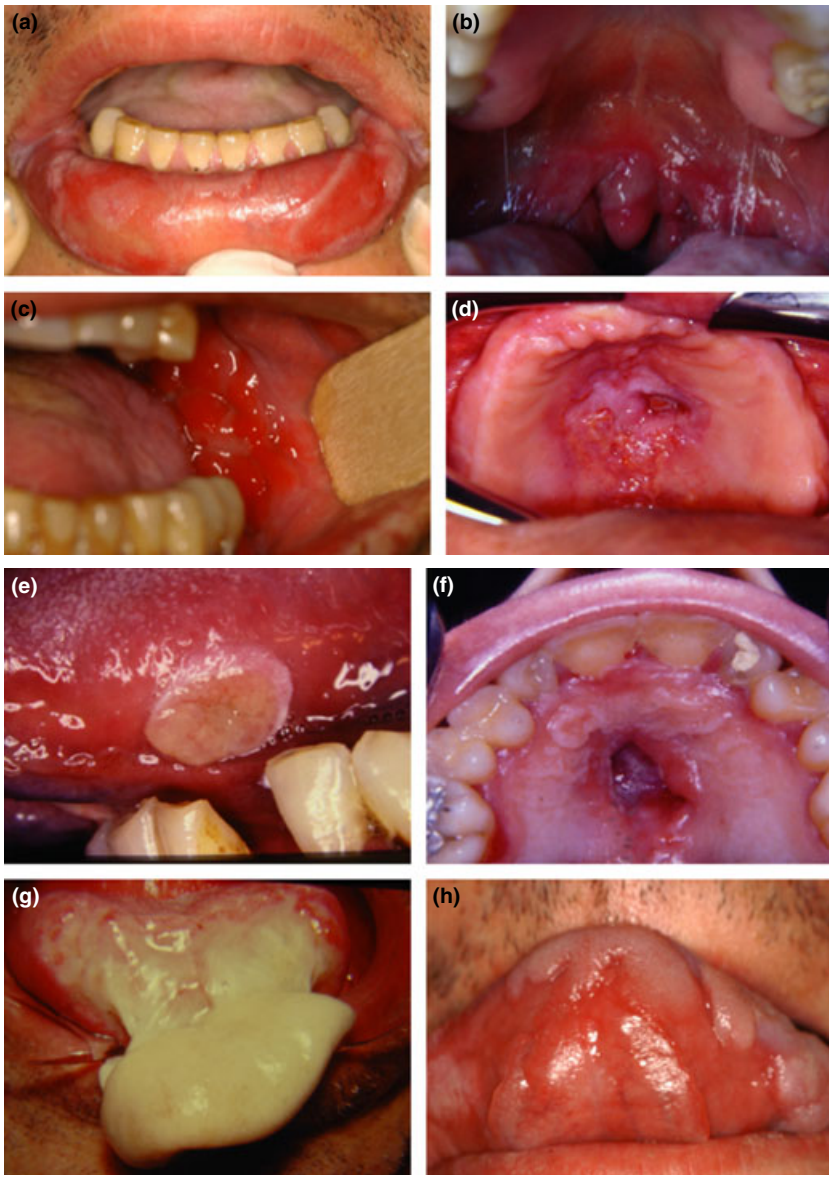

Figure 1 (**a**) whitish and erythematous mucosal patches of the lower labial mucosa. (**b**) ulcerated lesion of the soft palate and uvula with a surrounding erythematous area. (**c**) ulcer of the buccal mucosa. (**d**) typical aspect of syphilitic gumma involving the middle hard palate. (**e**) ulcer of the left margin of the tongue (**f**) deep ulcer of the middle hard palate. (**g**) extensive substance loss of the anterior part of the tongue. (**h**) polymorphous and diffuse keratotic lesions of the tongue

Physical examination showed an ulcerated lesion of the soft palate with a surrounding erythematous area, which extended to the uvula and the tonsillar pillars. The patient referred slight fever during the last 3 weeks before our first examination. An oral biopsy, VDRL, and TPHA tests were consistent with secondary syphilis. The patient was treated with 1 200 000 UI of benzylpenicillin benzhatine twice a week, and the lesions healed in 4 weeks.

Case 5 – In 2011, a 68-year-old Caucasian man was referred to our unit with a history of a 6-week painless ulcer of the soft palate and loss of weight around 6 kg during the last 6 months. An oral biopsy and VDRL and TPHA tests were positive, and therefore, we made a diagnosis of secondary syphilis. The patient received 1 200 000 UI of benzylpenicillin benzhatine twice a week, and, 5 weeks later, the lesions disappeared.

Case 6 – In 2007, a 29-year-old Caucasian man was referred to our unit with a chronic ulcer of the buccal mucosa (Figure 1c). The patient was under steroids therapy for rheumatoid arthritis. Physical examination revealed a chancre of the buccal mucosa associated with a suppurative cutaneous lymphadenitis that probably reflects secondary infection of the oral lesion. We performed an oral biopsy and VDRL and TPHA tests that were consistent with a diagnosis of primary syphilis. The patient was treated with 1 200 000 UI of benzylpenicillin benzhatine twice a week, and subsequently the lesion healed.

Case 7 – In 1997, a 70-year-old Caucasian man was referred to our unit for a chronic granulomatous lesion of the palate (Figure 1d). Physical examination showed the typical syphilitic gumma of the hard palate with a diameter of 4 centimeters. He also had a maculo-papular rash of the palms and soles. VDRL and TPHA tests were positive. Tertiary syphilis was diagnosed. The patient received 1 200 000 UI of benzylpenicillin benzhatine twice a week.

Case 8 – In 2005, a 34-year-old Caucasian woman was referred to our unit with an ulcerated lesion of the tongue (Figure 1e). Physical examination revealed an ulcer of the left edge of the tongue of 1 cm in diameter with the appearance of an oral cancer lesion. For this reason, a biopsy was performed, but the histopathology showed an unspecific inflammatory infiltrate. Moreover, she had papular lesions on the palms and soles. VDRL and TPHA tests were positive. Secondary syphilis was diagnosed. The patient received 1 200 000 UI of benzylpenicillin benzhatine twice a week and 3 weeks later the lesion healed.

Case 9 – In 2010, a 25-year -old Caucasian woman was referred to our unit with a history of a several week symptomatic ulcer of the palate (Figure 1f). The patient was treated for a dental abscess, but the lesion progressed to a very deep painful ulcer of the hard palate. She also had maculo-papular lesions of the trunk, palms, soles, and genitals. A biopsy was performed, and VDRL and TPHA tests were consistent for the diagnosis of secondary syphilis. The patient received 1 200 000 UI of benzylpenicillin benzhatine twice a week.

Case 10 – In 1994, a 70-year-old Caucasian man was referred to our unit with erosive lesions of the oral cavity and palate perforation. Three years previously, he had been operated on for heart failure caused by syphilitic arteritis. The anamnesis revealed an inadequate antibiotic therapy. A physical examination showed reddish erosive lesions of the palate with a gumma of the palate with bone perforation. The patient also had disseminated lesions of the trunk, palms, and soles. We performed a biopsy and VDRL and TPHA tests. A diagnosis of tertiary syphilis was made. The patient received 1 200 000 UI of benzylpenicillin benzhatine twice a week.

Case 11 – In 1996, a 65-year-old Caucasian man was referred to our unit with a necrosis of the tongue (Figure 1g). He had an acute myocardial infarction caused by syphilitic arteritis. The anamnesis revealed a dose of inappropriate penicillin therapy administered a few years previously. Physical examination showed a wide substance loss of the tongue secondary to syphilitic arteritis necrosis. We performed an oral biopsy. VDRL and TPHA tests were consistent for the diagnosis of tertiary syphilis. The patient received 1 200 000 UI of benzylpenicillin benzhatine twice a week.

Case 12 – In 2004, a 35-year-old Caucasian man was referred to our unit with a history of 3 week multiple ulcerated lesions and mucosal patches of the oral cavity (Figure 1h). Physical examination showed several ulcerated lesions involving the labial and buccal mucosa, tongue, and palate. He also had papular lesions of the genitals. We performed an oral biopsy of the lesions, but the histopathological examination revealed an unspecific inflammatory infiltrate. VDRL and TPHA tests were positive. Secondary syphilis was diagnosed. The patient received 1 200 000 UI of benzylpenicillin benzhatine twice a week, and the lesions disappeared after 4 weeks.

Discussion

Syphilis continues to be a major global health threat causing an estimated 12 million infections each year (World Health Organization, 2001). The increase in cases of syphilis over the last decade necessitates a renewed awareness of this infection and its varied manifestations.

There are two types of syphilis: congenital, transmitted vertically by transplacental spread and acquired syphilis, which is sexually transmitted (Scott and Flint, 2005) (Little, 2005).

The clinical manifestations of acquired syphilis, on the basis of its activity and infectivity phases, are classified into three well-described stages: primary, secondary, and tertiary that have important and different clinical, public health, and surveillance implications (Bruce *et al*, 2009).

Primary syphilis is mainly associated with a single or multiple lesions known as a chancre that occurs at the site of penetration of the organism into the mucosa (Bruce and Rogers, 2004). The sites are usually genital but can also be extra-genital, such as anus, fingers, nipples, lip, tongue, and tonsils (Goh, 2005). The majority of extra-genital chancres occur in the mouth (40–70%) (Kent and Romanelli, 2008). The chancre lesion is a painless and highly infectious indurated ulcer with a raised border usually associated with regional lymphadenopathy that occurs in up to 80% of cases approximately 7–10 days after the chancre appears (Chapel, 1978). In untreated individuals, treponemas proliferate in the chancre and are carried via lymphatic vessels to the bloodstream, from where they disseminate throughout the body (Baughn and Musher, 2005).

Secondary syphilis is a systemic disease and occurs approximately 2–12 weeks after the primary lesion (Scott and Flint, 2005) (Woo, 2012) where patient often presenting with a variety of symptoms, such as malaise, sore throat, headache, weight loss, low-grade fever, lymph node enlargement, pruritus, muscle aches, in addition to the dermatological manifestations (Baughn and Musher, 2005). The earliest expression of this stage is often a symmetric generalized rash involving the entire trunk, and the extremities including the palms of the hands and the soles of the feet. Other manifestations are condylomata lata, subclinical hepatitis, 'moth-eaten', and oral involvement. In particular, oral lesions arise in a high percentage of patients and are rarely the only manifestation of infection (Leão *et al*, 2006). The oro-pharyngeal examination may show highly non-specific features (Ficarra and Carlos, 2009): mucous patches, ulcers, papules, plaques often associated with a non-specific pharyngitis, tonsillitis, and laryngitis, sometimes also presenting as isolated cervical lymphadenopathy (van Crevel *et al*, 2009). Because this stage has a multitude of diverse presentations, syphilis is labeled the 'great imitator' (Domantay-Apostol *et al*, 2008).

After the secondary stage, syphilis, if untreated, becomes latent and is detectable only by serological testing. For the first year, previously 4 years (US Department of Health, 1962) and still 2 years in some countries (Parkes *et al*, 2004), latent syphilis is described as early latent and may lapse or relapse into the secondary stage (Read and Donovan, 2012). In this stage, the patient must have no signs of the primary or secondary disease and must have a positive syphilis serology.

Following this phase, syphilis is classified as late latent (the disease becomes non-infectious), during which time

sexual transmission is unlikely, but persons may develop tertiary syphilis, which can include neurological, cardiovascular, and other life-threatening complications (Leão *et al*, 2006).

Tertiary syphilis is characterized by three main manifestations: gummatous syphilis, neuro-syphilis and cardiovascular syphilis (French, 2007). A gumma is a painless granulomatous-like lesion usually localized on the skin, bone, and liver, but gumma lesions can affect any organ (Kampmeier, 1964). In the oral cavity, the gumma may affect the palate (midline), tongue or tonsils. Atrophic or interstitial glossitis is also described in some case reports (Captline *et al*, 1970) as well as salivary gland (parotid) involvement (Hira and Hira, 1984). There may be eventual bone destruction, palatal perforation, and oro-nasal fistula formation (Leão *et al*, 2006). When the infection involves the jaw, there is extensive osteonecrosis, characterized by pain, swelling, suppuration, and sequestration; this lesion can ossify, and the affected area may be similar to an osteogenic sarcoma (Greenberg *et al*, 2008).

Among the extra-genital sites of involvement, the oral cavity plays a pivotal role in diagnosis of the disease: dentists are usually the first clinicians to examine the oral lesions.

Because of the heterogeneity of the oral clinical aspects, the differential diagnosis includes a huge groups of diseases: traumatic or cancerous or non-specific inflammatory ulcers, autoimmune (pemphigus/pemphigoid) or immune-related lesions (lichen planus, erythema multiforme), traumatic (frictional keratosis) or hyperplastic/dysplastic plaques (leucoplakia), and other infectious diseases such as tuberculosis, deep fungal, herpes lesions and hairy leucoplakia.

The cases described from our database confirm that oral manifestations of syphilis are multiple and highly variable, and often detected in secondary stage. Only the 8% of patients and the 25% had, respectively, a primary and tertiary lesions. The evaluation of the morphology of the oral lesions in all stages of the disease revealed peculiar data. In line with the literature, primary syphilis is detected as ulcer in all patients, while secondary syphilis is detected as ulcer in about 50% of cases. In contrast to published data, mucosal patches are detected in only the 16% of patients and any evidence of leukoplakia-like lesions. Interestingly, case 2 affected by syphilis in secondary stage mimicking a blistering mucositis is never described in the current literature up to the paper by Mignogna *et al* (2009). Another interesting data are the necrosis of the dorsum of the tongue in patient 11 with tertiary disease.

Generally, the diagnosis of syphilis requires a knowledge of the patient's sexual history, physical examination, and an interpretation of serological and microbiological findings. The diagnosis is often made on clinical and serological grounds without recourse to biopsy.

In the oral cavity, clinical features are often non-specific, lesions could be not synchronous to skin manifestations. Anamnestic data are often difficult to recover, and patients are anxious toward a possible diagnosis of cancer. Frequently, a biopsy could help to proper manage syphilis patients.

The most frequently used approach is serological testing (Ratnam, 2005). Non-treponemal and treponemal serological tests are considered the standard detection methods in the US for all stages of syphilis (Golden *et al*, 2003).

The non-treponemal tests become positive 1–4 weeks after the appearance of the primary lesion, and 6 weeks after exposure. The most commonly used is the VDRL test and its simplified version, the RPR, which are the method of choice for follow-up testing during and after treatment (Scott and Flint, 2005).

The treponemal tests are used mainly as confirmatory tests to verify reactivity in non-treponemal tests. The most common are the FTA-ABS and TP-PA tests.

Recently, the availability of automatable treponemal enzyme and chemiluminescence immunoassays (EIA/CIA) has led some laboratories to adopt a reverse sequence of screening in which a treponemal EIA/CIA is performed first, followed by the testing of reactive sera with a non-treponemal test. The Center for Disease Control and Prevention (CDC) has reported that when the reverse sequence is performed, there is a high percentage of false-positive test results, in particular in the low prevalence syphilis population (CDC, 2011). For this reason, the CDC continues to recommend that non-treponemal tests be used to screen for syphilis, and treponemal tests be used to confirm the diagnosis to minimize false-positive results in the low prevalence population. However, if the reverse sequence is used, the CDC suggests that a specimen with reactive EIA/CIA results be tested reflexively with a non-treponemal test. If the test results are discordant, the specimen should be tested using the TP-PA test as a confirmatory treponemal test.

Historically, the treatment of early stage of syphilis provides benzathine penicillin G as the most frequently used antibiotic agent. According to the Epidemic Prevention Bureau of the US Ministry of Public Health, tetracycline, azithromycin, and doxycycline are alternatives to penicillin G benzathine if patients reveal any allergy. However, resistance to azithromycin has emerged rapidly. There is insufficient evidence from randomised controlled trials to determine whether azithromycin or penicillin G benzathine is the preferred treatment strategy in early syphilis. The decision to prescribe either azithromycin or penicillin G benzathine should be based on the cost effectiveness, safety and treatment preference (Bai *et al*, 2012).

In conclusion, our report confirms what widely reported in the literature: syphilis has the unique feature to imitate several diseases. In our experience, we performed always both serological tests and biopsy in every questionable cases from diagnostic point of view and/or in patients with unusual course of the disease with chronic oral lesions that not heal in 3–4 weeks.

Further researches are needed to assess better diagnostic tools, the proper treatment protocols both in early and late syphilis immunocompetent and immunosuppressed patients with evidence from multicentre controlled trials.

Author contributions

Stefania Leuci and Stefano Martina have made the research design, drafting the paper and revising it critically. Daniela Adamo, Elvira Ruoppo and Roberto Sorrentino have made the acquisition of data. Andrea Santarelli and Gianfranco favia have

selected and classified patients. Michele Davide Mignogna revised critically the paper.

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