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SCIENTIFIC LITERATURE

CASE REPORT

"A Night with Venus, a Lifetime with Mercury" Syphilis – The Overlooked Disease

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ABSTRACT

Syphilis is a notifiable Sexually-Transmitted Disease (STD) caused by the anaerobic spirochete Treponema Pallidum. Untreated syphilis not only causes severe medical complications: the disease also facilitates the transmission of HIV in cases of unprotected sex. Men who have Sex with Men (MSM) constitute a high-risk group. Syphilis is still shrouded in stigmatization despite a low-cost treatment with antibiotics.

The oral cavity is the most common extragenital site for primary syphilis, but the disease is often overlooked or misdiagnosed as an asymptomatic, non-specific oral ulceration. Through early diagnosis, the dentist plays an important role in reducing the risk of transmission of both syphilis and HIV. An overview with focus on the oral manifestations of syphilis is presented with an illustrative case.

Introduction

Syphilis (lues) is a Sexually Transmitted Disease (STD) caused by the Spirochete Treponema Pallidum. The main transmission is through genital contact (approx. 85%) or via extra-genital inoculation (oral, anal) through broken skin or mucous membrane [1-3].

The disease spreads amongst humans and can affect all organs in the body [4]. Since the turn of the millennium a vast increase has been noted in the number of reported cases of syphilis, not only in the USA, Canada and several Western European countries, but also in Eastern Europe, Russia, and China [5]. In 2008, ten million cases were diagnosed according to the WHO, and in 2015, 777 new infections were reported in Denmark [6,7].

Not only is syphilis very infectious, it also facilitates the transmission of other STD´s, such as HIV, in cases of unprotected sex. Since the first sign of extragenital syphilis may present as a non-specific lesion in the oral mucosa, it is of the outmost importance that the dentist is familiar with the differential diagnosis [2,4,5].

The following is an overview of the disease with emphasis on the oral manifestations, followed by a case report to illustrate the challenge in reaching the right diagnosis.

The Origin of Syphilis

The origin of syphilis is unknown. However, the first recorded epidemics of syphilis date back to the end of the 14th century, shortly after the return of

Christopher Columbus´s voyage to America. The theory is that the disease was brought from the "New World" via the "Conquistadores" to Europe where it spread from Napoli up through Europe via homebound German and Swiss mercenaries [3,8]. This is supported by the first illustration of syphilis from 1496, Albrecht Durer´s "Syphilitic Man", a wood carving of a homebound syphilis-stricken "Landsknecht" (mercenary) [8]. Others maintain, however, that Syphilis was endemic to Africa and brought to Europe much earlier, but not acknowledged prior to the outbreaks [9,10].

Many epidemics of "the French disease" have since struck Europe [8]. Throughout the 18th century syphilis was treated in vain with mercury, hence the adage "A night with Venus, a lifetime with Mercury", only to be replaced in 1910 by Arsphenamine (Salvarsan), an arsenic-containing drug [11,12]. Only in 1928, after the discovery of penicillin, was an antibacterial cure finally available. Despite a drastic drop in the number of cases following World War II, syphilis underwent a renaissance at the turn of the millennium in close conjunction with the emergence of the venereal disease Human Immunodeficiency Virus, commonly known as HIV [4,5].

1. Clinical presentation

There are four stages of acquired syphilis: primary, secondary, latent, and tertiary syphilis, in addition to congenital syphilis [1-4].

1.1. Primary syphilis: This is characterized by a chancre, a small painless ulcer/erosion, at the site of inoculation (60%) and regional lymphadenopathy (80%) following an incubation period between one week and 3 months [1,2,5,13,14]. Most chancres are genital, whereas extragenital chancres only account for 12-14%. An oral chancre represents inoculation via oral sex, kissing or other forms of contact with an infected area [1,2,5,14,15].

The clinical manifestations of both primary and secondary syphilis can be very varied and are easily mistaken for other diseases, hence the nickname "the great imitator" [11]. Initially, the chancre is macular (flat), followed by a papular (raised), indurated, erythematous appearance with a central ulceration [13]. Solitary chancres appear in 60% of cases and 70% are asymptomatic [16]. Despite its humble appearance the lesion is highly contagious. Orally, the most common locations are the tongue, palate, gingiva and lips. The upper lip is mostly affected in men and the lower lip in women. After 2-8 weeks, the lesion heals spontaneously without scarring. Only 30-40% of primary infections are diagnosed (Figure 1) [15].

Primary syphilis

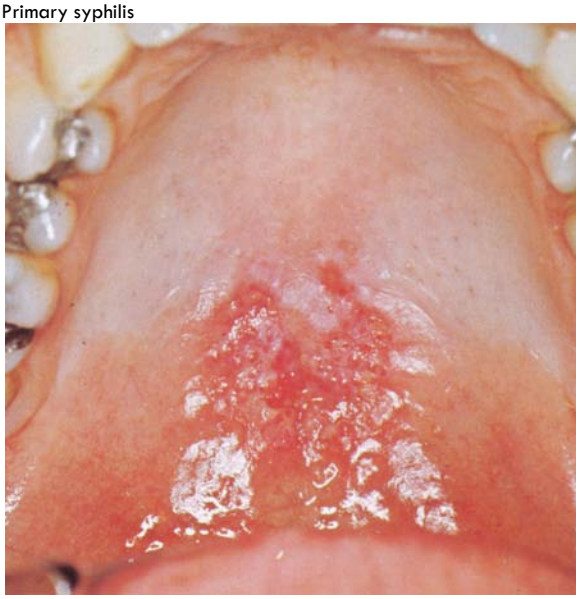


Figure 1: Palatal chancre in a 23-year-old man. From "Atlas of Oral Diseases" JJ Pindborg, 4th. ed., Munksgaard.

1.2. Secondary syphilis: Develops 1-3 months later. From having been restricted in the primary phase to the chancre and regional lymph nodes, the Treponema bacteria has now spread to the whole body via the lymphatic system and blood stream causing 1) non-specific symptoms of infection (fever, lymphadenopathy, headache, pharyngitis) 2) mucocutaneous changes (maculo-papular, non-pruritic rash of the palms and soles (75%), and patchy hair loss, defluvium, of the scalp, beard, and eyebrows (5-6%) [5,13,17] 3) systemic symptoms (manifestations of viscera simulating hepatitis, nephritis, osteitis, arthritis and meningitis in addition to visual disturbances and photophobia) [2]. Approx. 30% of secondary syphilis cases develop mucous patches, painful, grey-white pseudomembranous, slightly elevated lesions, circumscribed by a red halo

[15,18]. Several lesions are usually present, forming "snail track ulcers" resulting from coalescence of the smaller elements, typically seen on the palate, tongue and sulcus, simulating leukokeratosis [5]. In rare cases, condylomata lata, flat, broad, moist, papules, may be present on the palate and labial commissures, simulating fungal lesions [14]. Differential diagnosis to consider are: oral candidiasis, erosive lichen planus, leukoplakia, aphthous stomatitis, herpetic gingivostomatitis, erythema multiforme exudativum, squamous cell carcinoma [14,15,17]. Untreated ulcers regress within 3-6 weeks.

1.3. Latent syphilis: This is a dormant period free of clinical signs of syphilis. A blood test, however, will remain positive. Up to 30 years may pass between the secondary and tertiary stage [2]. Only 35% of cases progress into the tertiary stage [19], usually because the infection is diagnosed at an earlier stage. The tertiary stage is divided into three forms: gummatous syphilis, neurosyphilis and cardiovascular syphilis [8]. "Gumma/gummata" is a proliferative, granulomatous, indurated infiltration, which due to vasculitis (arteritis obliterans) may result in necrosis [18] and destruction of the surrounding tissue anywhere in the body (Figure 2) [2,5].

Gummata

Figure 2: Patient with tertiary (gummatous) syphilis. Buste, Museé de l´Homme, Paris.
Reported cases of syphilis in Denmark from year 2000 to 2015.

In the mouth, gumma is usually seen on the hard palate, causing oronasal perforations, but may occur on the soft palate, lips, and tongue [14]. Atrophic glossitis, with loss of the filiform and fungiform papillae, or interstitial glossitis, with fissuring and in duration, may occur together with lingual leukoplakia, suspicious for carcinoma [14,19].

The typical infections of the central nervous system are meningitis, general paresis, or tabes dorsalis (demyelination of the spinal cord causing pain and loss of proprioception), Argyll Robertson pupils, seizures and dementia, whereas cardiovascular syphilis comprises a ortitis and aorta aneurysm [2,5].

1.4. Congenital syphilis: This is a profoundly debilitating disease reflecting variable stages of vasculitis, which, if left untreated, will lead to tertiary syphilis. Vertical transmission occurs via the placenta or at delivery in cases of genital lesions. The presence of fetal IgM is indicative of infection, since IgM does not cross the placenta [2,13]. Characteristic odontogenic features are: Hutchinson´s incisors, Mulberry molars, perioral rhagades, and palatal gumma. Saddle nose, neurosyphilis, mental retardation, deafness, hydrocephalus and hepatosplenomegali are just some of the systemic complications to be encountered [2,13,14,20].

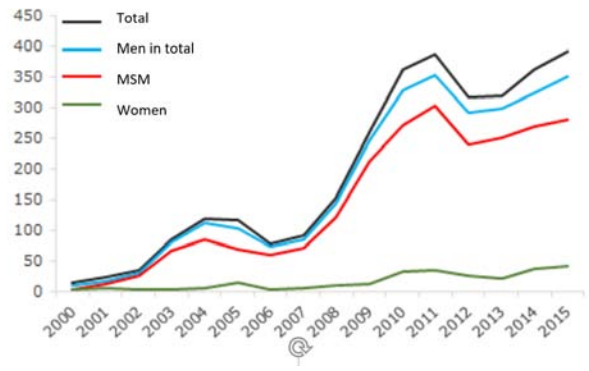


Figure 3: Marked increase in the number of reported cases of syphilis between 2007 and 2011, and yet a peak in 2015. The number of syphilis infected MSM (men who have sex with men) is significantly higher than the number of syphilis positive women. Therefore, homosexual males constitute the largest risk group.

Epidemiology of Syphilis and Pregnancy Screening in Denmark

Since the turn of the millennium, the number of Danish cases of sexually transmitted syphilis recorded by the nationalsurveillance system (MSI), stewarded by Statens Serum Institut (SSI), and has increased significantly (Figure 3). From only 34 recorded notifications in 1999, the curve has been on the rise since 2007, peaking in 2011 with 434 notifications and again in 2015 with 391 notifications in 383 patients. However, 386 cases lacked notification to the MSI, raising the figure of newly acquired syphilis to 777 infections in 742 patients [7,21]. Between 2013 and 2015, the median age for men infected with syphilis increased from 38 years to 41 years and for women from 30 years to 32 years, both sexes representing the sexually active and childbearing ages. The distribution according to gender of the 383 patients shows a male dominance of 89% (342 men), of which MSM account for 80% (273 men), thus constituting the high-risk group. Only 41 patients (11%) were women [7,21].

The prevalence of syphilis may reflect an increase in high risk sexual behavior due to cures or much improved treatment options for STDs such as HIV, which is no longer fatal. A reduction in the use of protective measures may also reflect a lack of understanding and awareness that oral sex is just as "unsafe" as ano-genital sex [4,6,20].

Syphilis is most contagious in the primary and secondary stages. Having unprotected sex with a syphilis-infected partner increases the risk of contracting the infection by 30-50% [13]. Likewise, syphilis-induced genital ulcers increase the risk of contracting or infecting a partner with HIV with a factor of 2-5 [22]. In 2015, 40% of MSM with syphilis were HIV positive [7]. The incidence of co-infection of HIV and syphilis, however, does not mean that the STIs were contracted at the same point in time. It merely indicates that the STIs occurred within in the same period of observation. Thus, of a total of 94 HIV positive men who contracted syphilis in Denmark in 2016, 10 men (11%), of whom 8 were MSM, were diagnosed for the first time as co-infected with syphilis and HIV. The remaining 84 men (89%), of whom 76 were MSM, were previously diagnosed as HIV positive prior to contracting syphilis [23].

Pregnancy screening for syphilis was reintroduced in Denmark in 2010, following two cases of congenital syphilis [21]. The screening, which also includes Hepatitis B and HIV, is performed at the first prenatal checkup. Early diagnosis is important because the antibiotic treatment will affect both mother and fetus. Due to increased immigration, it is important to establish whether the mother has been part of a screening program, because syphilis is not necessarily recognizable at birth [13].

Case Report

A 45-year-old Caucasian male painter was referred from his dentist regarding a two-month history of persistent sores on his lateral tongue and the corners of his mouth, and the lingual frenulum. Furthermore, a lesion of the hard palate had been observed.

At the same time, the patient had complained of flu-like symptoms, sore throat and malaise but no fever. Recently, several blood tests had been taken by his General Medical Practitioner (GMP), but the tests did not show any signs of infection. The patient described a habit of sucking his cheeks and lips and wore a dental splint against nocturnal bruxism.

1. General medical history

Some months previously, the patient had suffered from a rash on his hands and body. This had been interpreted as eczema against paint. Past medical history revealed only a gastric ulcer, and the patient had no known allergies and no reported usage of tobacco, alcohol or medication.

2. Clinical examination

Extra-orally: Slim, healthy looking male with no obvious lymphadenopathy. Intra-orally: The patient was fully dentate with adequate restorations. Small, slightly indurate, bilateral, symmetrical, erosions were present on the lateral borders of the tongue and the labial commissures along with a small ulceration on the middle of the lingual frenulum (Figure 4a-4e). The elements were between 2 and 6 mm in diameter, partly or

Ulceration of the mouth on presentation.

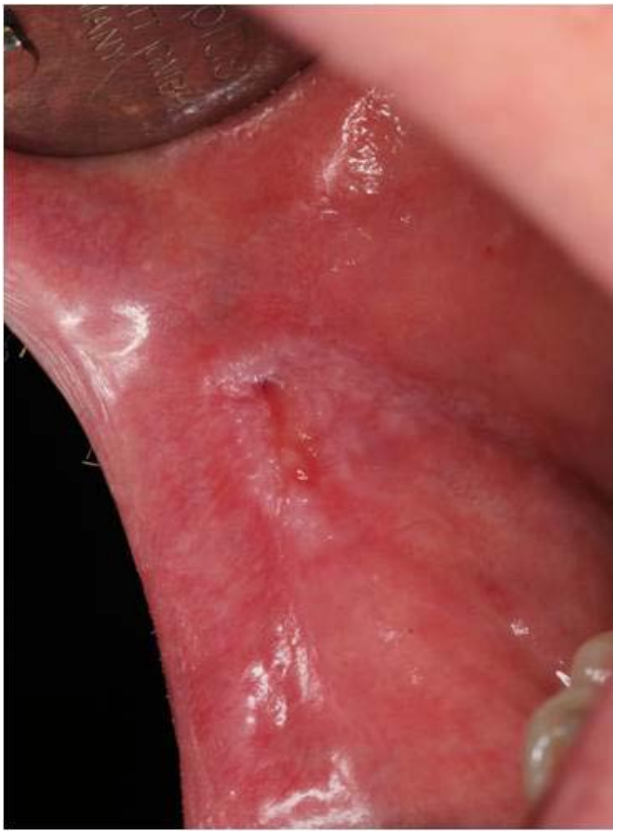


Figure 4(a): Ulceration related to labial commissures

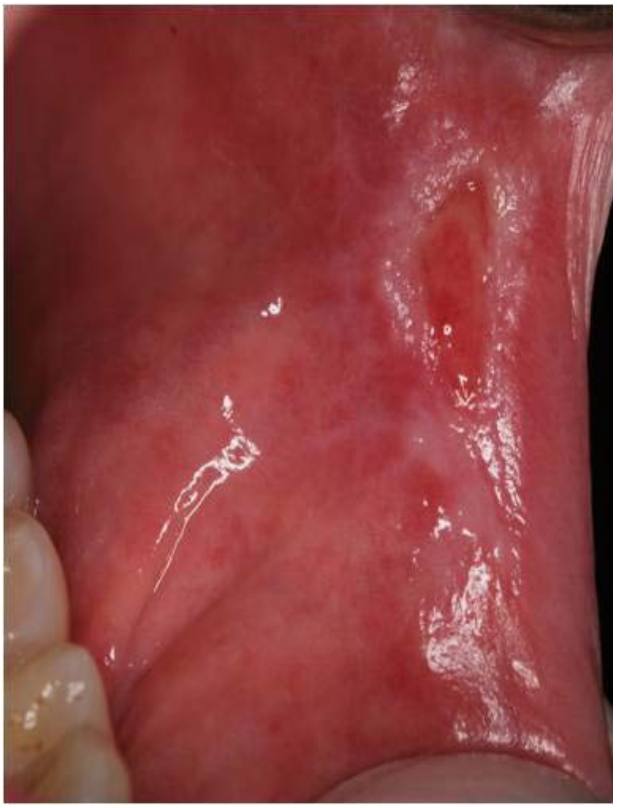


Figure 4(b): Ulceration related to labial commissures.

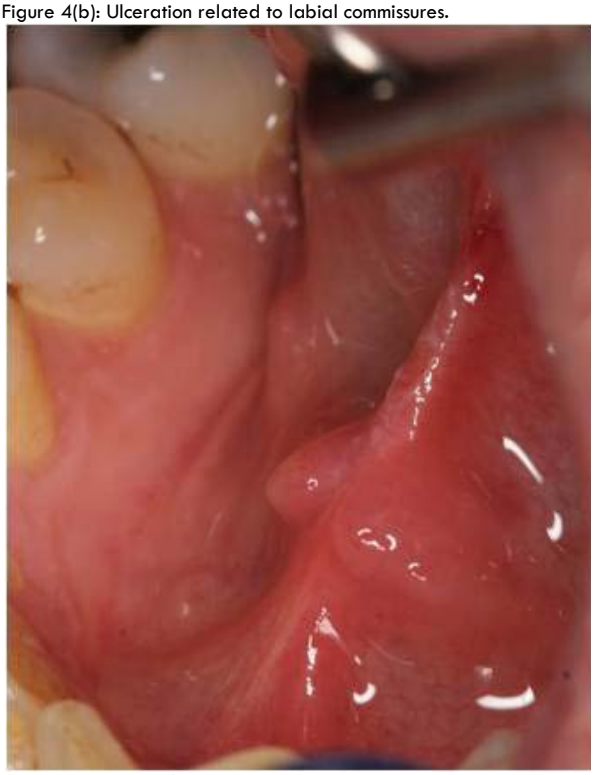


Figure 4(c): Lingual frenulum.

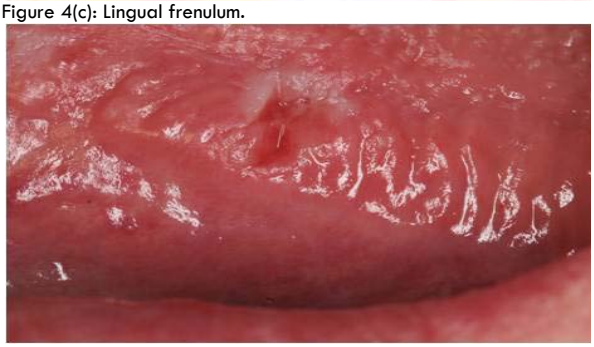


Figure 4(d): Bilateral tongue margins.

Figure 4(e):Bilateral tongue margins.

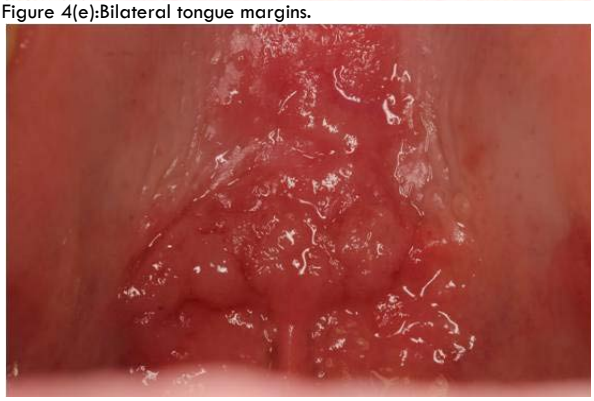
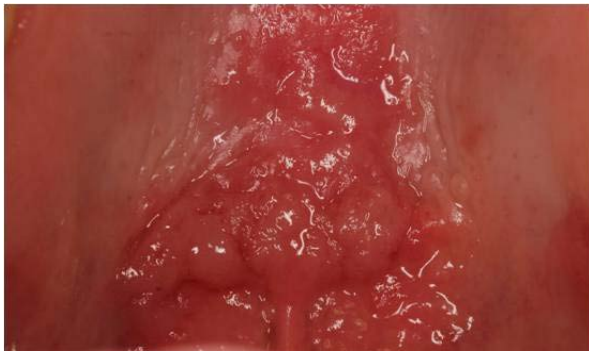


Figure 4(f):Multilobular erythematous lesion of the hard palate.



completely circumscribed by a white macular, hyper-keratinized zone with only slight soreness on palpation. In the center of the posterior 2/3 of the hard palate, a well demarcated 2,5 x 3 cm erythematous area was noted, consisting of multiple, soft, papillomatous/lobular, granulomatous elements with modest soreness on palpation (Figure 4f). An erythematous zone extended from the posterior border of the hard palate into the throat.

3. Tests

A swab was taken for Candida albicans, as well as biopsies of the lip and the hard palate for histological examination, including assessment for Human Papilloma Virus (HPV). No additional blood tests were taken until the final results from the GMP were known.

4. Test results and treatment

The mycotic test showed marked overgrowth of Candida albicans. Thus, antimycotic treatment was prescribed (Mycostatin mixtur®, 1 ml x 4 daily) for 2 weeks.

The pathology report for both biopsies excluded virus but described mucositis changes with areas of less acute inflammation, most profound in the palate. A close infiltration of plasma cells was present in both specimens, notably the palatal biopsy, which showed deep perivascular infiltration. These findings raised the suspicion of syphilis. Further staining for Treponema Pallidum was recommended and the patient was recalled for further serological testing for HIV and syphilis. At a follow-up ten days later, the patient had completed the anti-mycotic treatment and all the oral lesions had healed completely (Figure 5a-5f). On questioning, he confirmed his status as MSM, presently living in a stable relationship. Although the recent HIV test was negative, he agreed to be tested for syphilis, the result of which was positive.

The patient and his partner were referred to the regional clinic for STD´s for further treatment and completion of the notification of the disease. The drug of choice for treating primary and secondary syphilis is a single intramuscular injection of 2.4 million units of benzathine penicillin G, a long-acting drug which combines benzylpenicillin-benzathine with a local anesthetic. The protracted effect is sought because Treponema Pallidum divides slowly (30-33 hours) [13]. In cases of latent or tertiary (gummatous or cardiovascular) syphilis, the treatment is extended to weekly injections for 3 weeks. In cases of allergy to penicillin, doxycycline tablets (100 mg twice daily for 2 weeks) or tetracycline tablets (400 mg for 2 weeks) are recommended, extending to 3-4 weeks for the later stages [13,24]. Ceftriaxone has also been mentioned, but the optimal dosage and treatment duration is not yet established. A complication to the antibiotic treatment is the Jarisch-Herxheimers reaction, a toxic reaction resulting in flu-like symptoms, which is thought to be caused by the sudden release of cytokines in response to lipoproteins from ruptured Treponema bacteria. This should not be confused with allergy to penicillin [11,13,24].

The adequacy of the treatment is monitored through serological testing. Therapy has failed if the symptoms return or fail to improve. Likewise, if the titer of the nontreponemal test increases or does not decrease 4-fold within one year [13,2].

Discussion

Although the oral cavity is the highest-ranking location (40-75%) for extra-genital syphilis, it only constitutes 2-4% of all cases of primary syphilis [1,2,5], 60-70% of which remain undiagnosed. Despite the rarity of diagnosing a chancre in the dental chair, it is most relevant to include this differential diagnosis when presented with unusual patches and ulcerations in the oral cavity.

The clinical diagnosis is very difficult. The oral lesion is usually painless, and the patient often does not seek

Oral mucosa after antifungal treatment.

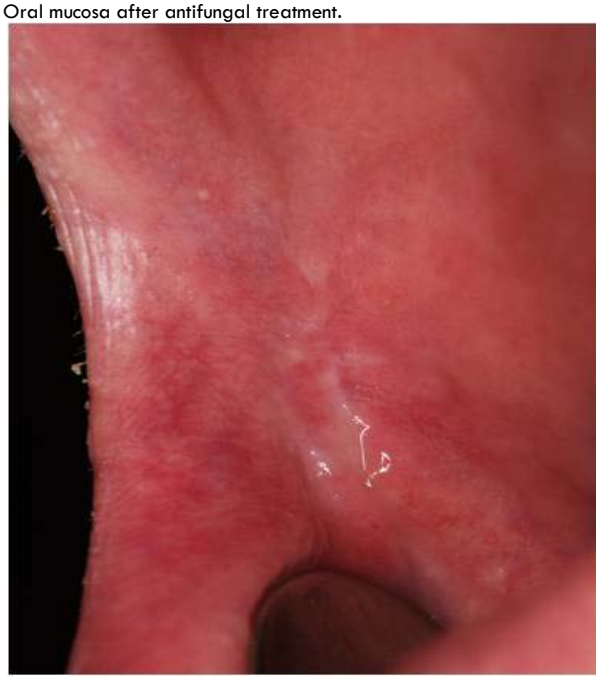


Figure 5(a): Healing of oral ulceration. Granulation tissue on left side of palate represents the biopsy site.

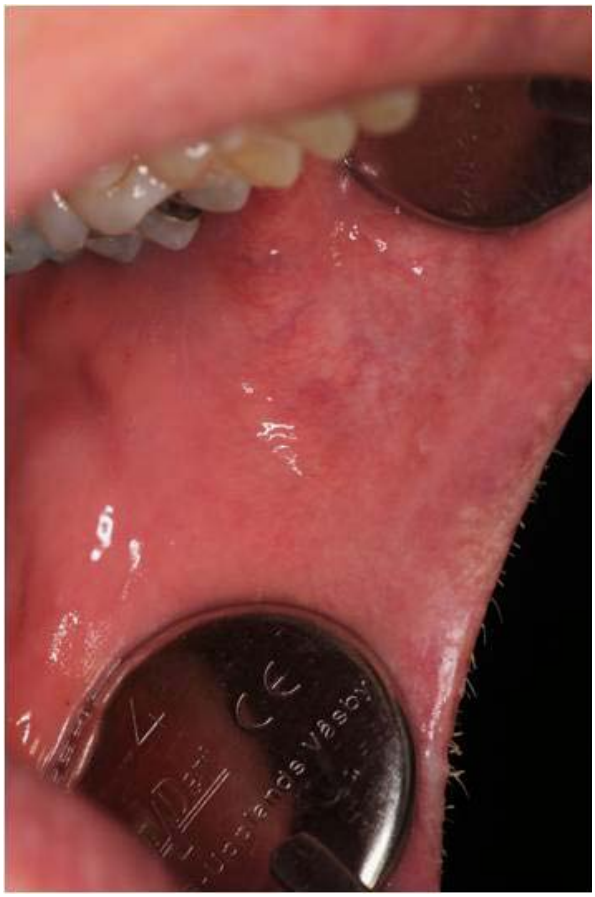


Figure 5(b): Healing of oral ulceration. Granulation tissue on left side of palate represents the biopsy site.

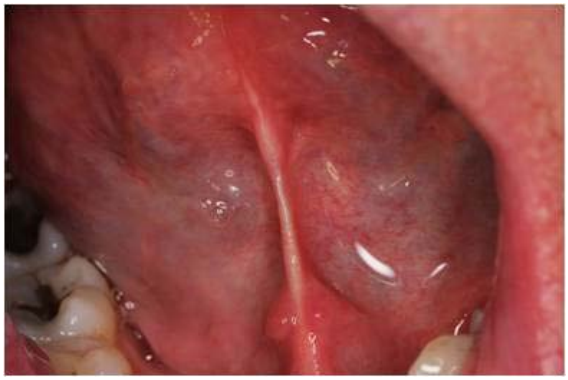


Figure 5(c): Healing of oral ulceration. Granulation tissue on left side of palate represents the biopsy site.

Figure 5(d): Healing of oral ulceration. Granulation tissue on left side of palate represents the biopsy site.

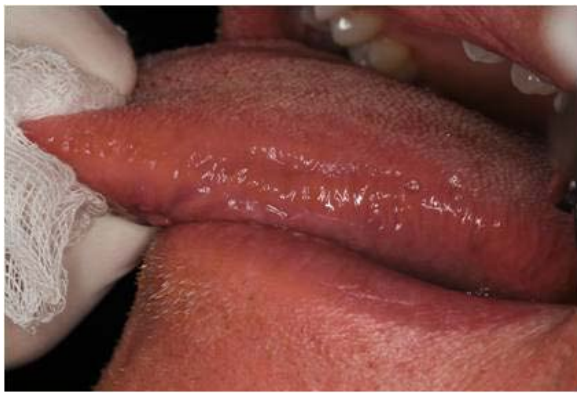


Figure 5(e): Healing of oral ulceration. Granulation tissue on left side of palate represents the biopsy site.

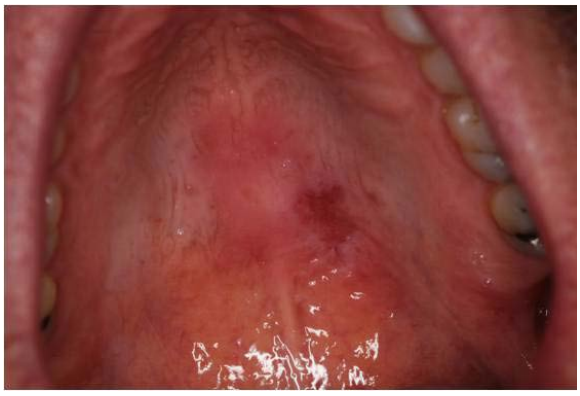


Figure5(f): Healing of oral ulceration. Granulation tissue on left side of palate represents the biopsy site.

professional advice because it heals quickly. Likewise, there is the risk of misdiagnosing the chancre for a more common lesion such as lichen planus, aphthous ulcer, herpes simplex or trauma. A wrong treatment strategy (e.g. use of topical steroid gel without a diagnostic biopsy) could easily be misinterpreted as a success because the chancre resolves on its own [2,19].

Whether our patient had previously experienced an oral chancre is unknown. The patient recalled calling his GMP two months earlier, due to a lingual ulcer. This was thought to be an aphthous ulcer and was treated with chlorhexidine mouthwash.

Histological picture of palatal biopsy.

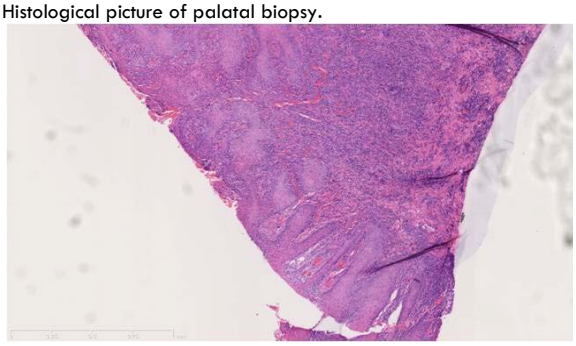


Figure 6a: Hyperplastic epithelium. Mixed inflammatory response with dominant plasma cell infiltrate of the stroma.

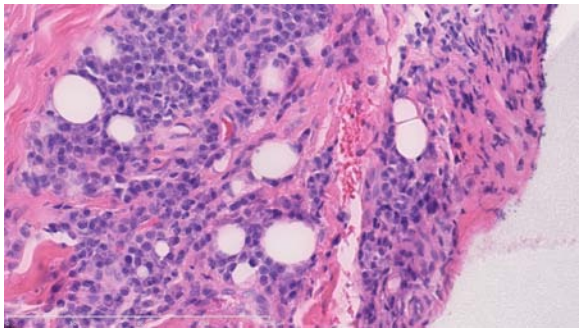


Figure 6b: Deep perivascular infiltrate of plasma cells.

At the time of referral, the patient was probably in the secondary stage of syphilis. He had for several weeks complained of a sore throat and "flu-like" symptoms (malaise, headache, muscle soreness) in addition to oral ulcerations. A rash had been noted on the body and hands four months earlier but was thought to be eczema. There were no complaints of defluvium. The erythematous popular /multilobular element of the palate, however, was very similar to the chancre seen in Figure 1.

The differential diagnosis of the mucous patches found on the tongue, labial commissures and lingual frenulum could be erosive lichen planus and trauma, as the patient had an oral habit of bruxism and sucking his cheeks and lips. The atypical, granulomatous, multilobular lesion of the hard palate raised the suspicion of viral or venereal disease.

Treponema pallidum

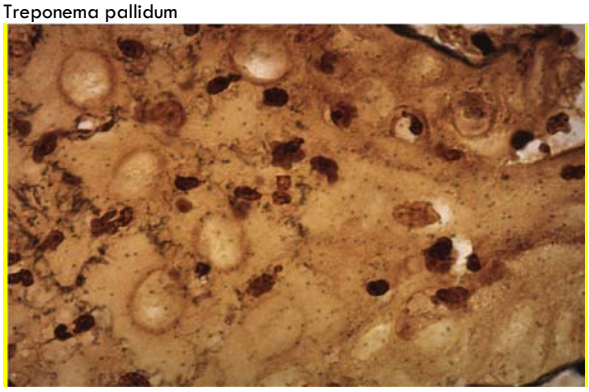


Figure 7: Warthin-Starry stain.100x enlargement. Thin spiral-shaped spirochetes (Treponema pallidum) with varying morphology. Placement of an arow is suggested as seen in figure 7

A fungal infection can worsen and change the clinical appearance of a mucosal lesion e.g. lichen planus [2]. A swab was taken to test for Candida albicans alongside the biopsies of the palate and labial commissure. The fact that all the mucosal elements had healed after the antimycotic treatment could, of course, be due to the antifungal treatment. However, the resolution of the oral manifestations could reflect the natural resolution of oral mucosal changes as seen in secondary syphilis which coincided with the antimycotic treatment.

Direct visualisation of the spirochete Treponema Pallidum requires fluid or tissue from syphilis sore to make the diagnoses. As opposed to many other bacteria, it cannot be cultivated for in vitro testing [5,15]. Detecting the spirochete is through either 1) Polymerase Chain Reaction (PCR), a DNA recognition of the microorganism, or 2) dark-field microscopy, which calls for an experienced examiner and a detectable number of Treponema spirochetes. Blood samples, however, can instead detect antibodies to the infection.

A combination of two types of serology test are used, the non-treponemic tests, which are inexpensive and

used for screening and follow-ups, and the treponemic tests, which are more specific and used to confirm the diagnosis following a positive non-treponemic test [5,15,17]. Our patient showed positive serology.

Correlating the clinical and pathological findings with the patient history raised the suspicion of secondary syphilis, which was later confirmed serologically and histologically (Figure 6,7).

Conclusion

Syphilis is a very contagious venereal disease which is often transmitted through direct contact with a genital lesion but can also occur through blood and saliva [20]. An oral chancre is usually indicative of unprotected sex, which increases the risk of HIV transmission.

Lacking a vaccine, early diagnosis and treatment is the present cornerstone to epidemic control of syphilis and the transmission of HIV. The dentist plays an important role in detecting primary and secondary syphilis.

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References

1. Vinals-Iglesias H, Chimenos-Kustner E. (2009). The reappearance of a forgotten disease in the oral cavity: syphilis. Medicina oral, patologia oral y cirugiabucal. 14: e416-e420.
2. Brad Neville, Douglas D, Allen Carl, Jerry Bouquot. (2009). Oral and Maxillofacial Pathology. 3rd ed: Saunders.
3. Farhi D, Dupin N. (2010). Origins of syphilis and management in the immunocompetent patient: facts and controversies. Clinics in dermatology. 28: 533-538.
4. Giovani EM, de Paula Neto ER, Vieira BC, de Andrade DM. (2012). Conventional systemic treatments associated with therapeutic sites of local lesions of secondary syphilis in the oral cavity in patients with AIDS. Indian journal of dental research: official publication of Indian Society for Dental Research. 23: 670-673.
5. Ficarra G, Carlos R. (2009). Syphilis: the renaissance of an old disease with oral implications. Head and neck pathology. 3: 195-206.
6. Solomon MM, Mayer KH, Glidden DV, Liu AY, McMahan VM, et al. (2014). Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 59: 1020-1026.
7. Cowan S, Hoffmann S,(2016). Case of measles in the Copenhagen area.
8. Eisler CT. (2009). Who is Durer's "Syphilitic Man"? Perspectives in biology and medicine. 52: 48-60.
9. Rothschild BM. (2005) History of Syphilis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 40: 1454-1463.
10. Tramont EC. (1995). Syphilis in adults: from Christopher Columbus to Sir Alexander Fleming to AIDS. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 21: 1361-1369.
11. Syphilis.
12. Stephane Gibaud, GJ. (2010). Arsenic- based drugs: from Fowler´s solution to modern anticancer chemotherapy. Topics in Organometallic Chemistry 32: 1-20.
13. Syfilis.
14. Pindborg JJ. (1985) Atlas of Diseases of the Oral Mucosa 4. edn.: Munksgaard;
15. Kelner N, Rabelo GD, da Cruz Perez DE, Assuncao JN, Jr., Witzel AL, et al. (2014). Analysis of nonspecific oral mucosal and dermal lesions suggestive of syphilis: a report of 6 cases. Oral surgery, oral medicine, oral pathology and oral radiology. 117: 1-7.

16. Kent ME, Romanelli F. (2008). Reexamining syphilis: an update on epidemiology, clinical manifestations, and management. The Annals of pharmacotherapy. 42: 226-236.
17. Alam F, Argiriadou AS, Hodgson TA, Kumar N, Porter SR. (2000) Primary syphilis remains a cause of oral ulceration. British dental journal. 189: 352-354.
18. Minicucci EM, Vieira RA, Oliveira DT, Marques SA. (2013). Oral manifestations of secondary syphilis in the elderly - a timely reminder for dentists. Australian dental journal. 58: 368-370.
19. Marx RE. Stern D. (2012). Oral and Maxillofacial Pathology. 2nd ed: Quintessence.
20. Jones L, Ong EL, Okpokam A, Sloan P, Macleod I. (2012). Three cases of oral syphilis - an overview. British dental journal. 212: 477-480.
21. Soborg B, Cowan S. Statens Serum Institut. (2011).
22. HIV Prevention Through Early Detection and Treatment of Other Sexually Transmitted Diseases -- United States Recommendations of the Advisory Committee for HIV and STD Prevention.
23. Statens Serum Institut. (2016).
24. Chandrasekar, PH Syphilis Treatment and Management.