

Oral Syphilis: A Series of 5 Cases

Moritz Hertel, Dr Med Dent, *Daniel Matter, Dr Med Dent, †
Andrea M. Schmidt-Westhausen, Prof Dr Med Dent, ‡
and Michael M. Bornstein, PD Dr Med Dent §

Syphilis is an infectious, usually sexually transmitted, disease caused by *Treponema pallidum*, subspecies *pallidum*. Because of the increasing prevalence in Europe during the past few years, dentists could be confronted with patients with oral manifestations of syphilis. Because oral lesions are highly contagious, it is vital to make the correct diagnosis quickly to initiate the proper therapy and to interrupt the chain of infection. We present the cases of 5 patients with syphilis-related oral lesions. These cases are representative because of their clinical presentation, age, and gender distribution and the diagnostic approach. The aim of the present report is to emphasize the importance of the dentist knowing and identifying syphilis in different stages to diagnose the disease and institute treatment at an early stage.

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Syphilis has some important implications for the dental team. First, syphilis can result in oral manifestations, the first and second stages of which are highly contagious. Second, the disease can be transmitted by direct contact with oral lesions, saliva, and blood. Third, additional sexually transmitted diseases (eg, gonorrhea) could be present and the risk of human immunodeficiency virus (HIV) infection could be greater. Finally, the dental team can play a role in making an accurate and early diagnosis and referring the patient for adequate treatment.

In the early years of the 20th century, extragenital lesions due to syphilis were not unusual and could be found anywhere on the body. Any indurated ulcer with regional lymphadenopathy should lead the physician to consider primary syphilis, regardless of the site.

During the previous century, the incidence of the formerly widespread disease declined until the nadir was reached in the mid-1980s. A correlation between the decline of the disease and the advent of the HIV prevention campaigns seems to be crucial.¹

Since the collapse of the Union of Soviet Socialist Republics in the 1990s, the incidence of reported cases

has increased, first in Eastern Europe, but more and more, also in Western Europe. The increasing incidence in the 1990s was attributed to sexual liberation. In contrast, sex tourism, freedom of travel, new contraceptives, and changing social conventions might have contributed to the noticeable increase in recent infections. HIV was a fatal disease in the 1980s; however, with the advances made in pharmaceutical research, this is no longer considered to be the case. Consequently, barrier methods such as condoms have been used less consistently, permitting the spread of disease. In addition, so-called safe sex practices, such as oral sex, are not regarded as a relevant transmission path for HIV. However, oral sex is the major cause of the oral manifestations of syphilis.

When syphilis became a notifiable disease in Germany in 2001, 1,697 new cases were reported and 1,379 of the infected patients were men. By 2004, the number of new infections had increased to 3,325. The number of women affected remained essentially constant. From 2004 to 2008, the number of cases was constantly high (3,000 to 3,500 per year). In 2009, 2,716 new infections were reported.² The latest data available have

*Resident, Charité Centre 3, Department of Oral Medicine, Dental Radiology and Oral Surgery, Charité Medical University Berlin, Berlin, Germany.

†Resident, Department of Oral Surgery and Stomatology, University of Bern School of Dental Medicine, Bern, Switzerland.

‡Professor, Charité Centre 3, Department of Oral Medicine, Dental Radiology and Oral Surgery, Charité Medical University Berlin, Berlin, Germany.

§Senior Lecturer, Department of Oral Surgery and Stomatology, University of Bern, School of Dental Medicine, Bern, Switzerland.

Drs Hertel and Matter contributed equally to this study.

Address correspondence and reprint requests to Dr Hertel: Charité Centre 3, Department of Oral Medicine, Dental Radiology and Oral Surgery, Charité Medical University Berlin, Almannshäuser Strasse 4-6, Berlin 14197, Germany; e-mail: moritz.hertel@charite.de
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revealed a new increase in the number of notified infections. In 2010, 3,033 patients with syphilis were reported; 1 year later, 3,698 infections were recorded, corresponding to a mean incidence of 4.5 cases/100,000 inhabitants and the highest number since the implementation of the notification requirement. Large cities such as Cologne, Frankfurt, and Berlin have reported a greater incidence (24, 21, and 18/100,000, respectively). Men were affected more than 14 times more often than women. Among those patients for whom information concerning the transmission path was available, 83.9% were men having sex with men.³

In Switzerland, laboratories and physicians have been required to report diagnosed cases of syphilis since 2006. The disease was not notifiable in Switzerland from 1999 to 2006. In the 1990s, the number of new infections decreased from 300 cases in 1990 to 50 cases in 1999.⁴ In 2006, 2009, and 2010, 182, 363, and 381 infections were confirmed by clinical and laboratory reports, respectively. The total number of reported cases has increased (657 in 2006, 792 in 2009, and 975 in 2010).⁵ The risk factors and distribution between the genders were similar to those in Germany. At 40 to 44 years old, men having sex with men are at the greatest risk of acquiring syphilis, indicating that promiscuous behavior is involved.⁶

The popularity of oral sex has been increasing in recent years—in part, because it is supposed to be a safer sex practice. Consequently, extragenital lesions, of which oral manifestations are the most frequent, have become more common.¹ Therefore, dentists can play a major role in detecting the disease.

In recent years, several reports have presented case series of patients with oral manifestations of syphilis.⁷⁻⁹ A review of syphilis cases was also published in 2005.¹⁰ In all of our 5 cases, the initial suspicion of syphilis resulted from the dentist's examination. The aim of the present report was to emphasize the importance of the dentist knowing and identifying syphilis at different stages, especially because the disease might temporarily only cause oral symptoms. In addition, it was our intent to highlight the importance of cooperation between dentists and infectious disease specialists to widen the patient's medical history and achieve rapid diagnosis and treatment.

Patients and Methods

Five patients with verified syphilis were identified from 2004 to 2011 in the Department of Oral Medicine, Dental Radiology, and Oral Surgery, Charité (Berlin, Germany), and the Department of Oral Surgery and Stomatology, School of Dental Medicine, University of Bern (Bern, Switzerland). In accordance with the World Medical Association Declaration of Helsinki on medical research protocols and ethics and because

of the retrospective nature of the study, an exemption was granted from the authors' institutions and no formal approval by the institutional review boards was necessary. The collected data were anonymized at the stage of extraction from the patient charts.

Case Reports

CASE 1

A 43-year-old male patient was referred to the Department of Oral Surgery and Stomatology, University of Bern, by his dental practitioner for an examination of a whitish, nonwipeable lesion on the left palate and a thickened lower labial frenum. His general medical history revealed that, 10 months previously, the patient had developed hearing loss on the left and progressively on the right side. An examination at the University's Department of Otorhinolaryngology, Head and Neck Surgery, confirmed the hearing loss, and a hearing aid was recommended.

When interviewed, the patient reported that about 2 weeks earlier, a similar lesion of the upper labial frenum had healed spontaneously. However, the lesions on the palate and the lower frenum persisted and were undergoing constant changes. The intraoral examination showed a mixed reddish and whitish, partially ulcerated, plaque at the markedly thickened labial frenum (Fig 1A). On the left part of the soft palate, an oval ulcer covered by fibrin with a diameter of about 10 mm could be seen (Fig 1B).

From the clinical viewpoint, recurrent aphthous ulcerations were initially considered. An excisional biopsy of the lower labial frenum was performed using a carbon dioxide laser with the patient under local anesthesia. The excised tissue was examined histologically after staining with hematoxylin and eosin. Histologic examination revealed infiltration by lymphoid cells, an increase in plasma cells, and several small lymphoepithelial islands. This unspecific inflammation led to an extended questioning of the patient, in particular relating to his sexual history. However, after several interviews, the sexual history remained unclear. Eventually, the patient was urged to undergo a serologic test for syphilis and HIV. The serologic results were positive for syphilis (*Treponema pallidum* particle agglutination assay [TPPA] positive; Venereal Disease Research Laboratory [VDRL] positive; and enzyme-linked immunosorbent assay positive for *Treponema pallidum* IgG and IgM; for additional details see the *Discussion* section), and negative for HIV.

Consequently, the patient was referred to the Department of Infectiology. Additional inquiry revealed that for the past couple of years, the heterosexual patient had had unprotected sexual intercourse with several women. Because of the oral lesions and the positive serologic results for syphilis, the diagnosis of

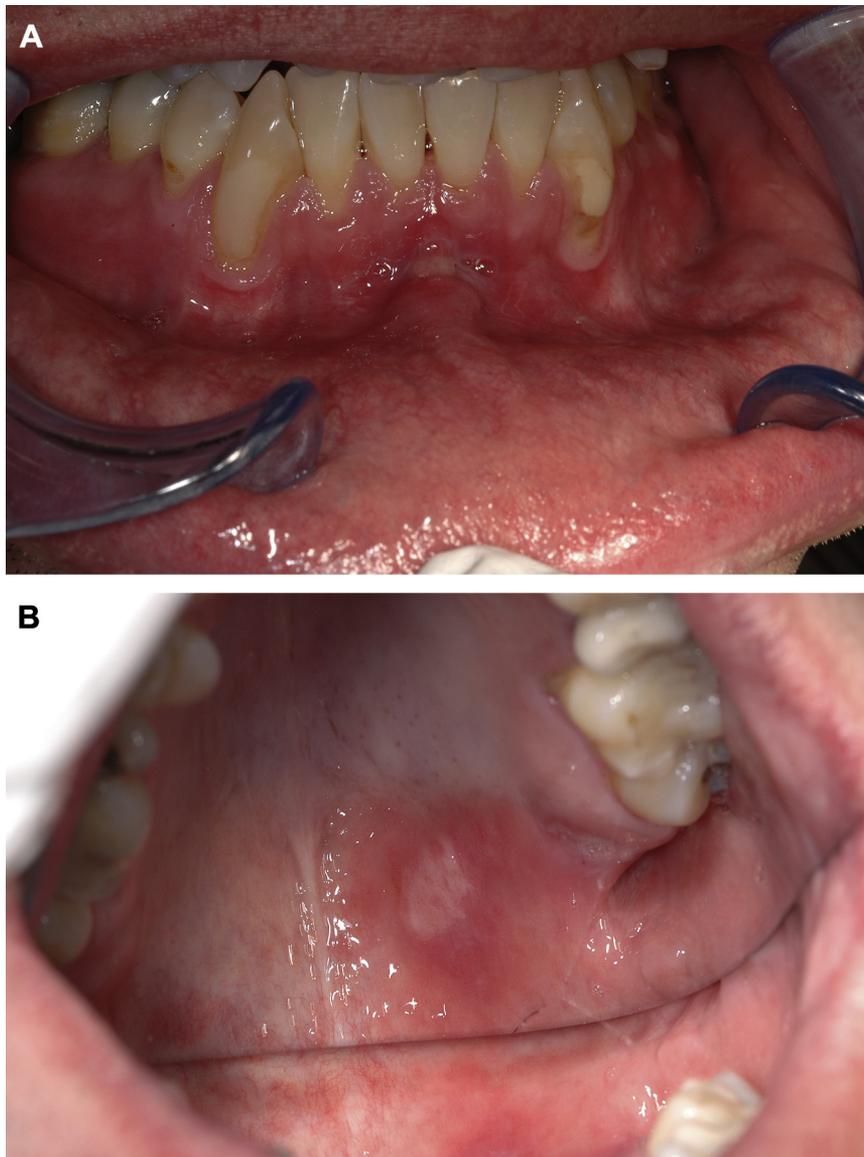


FIGURE 1. Patient 1. A, The lower labial frenum is swollen and shows a 4- to 5-mm ulceration covered by fibrin. B, Oval ulcer, 10 mm in diameter, of the left part of the soft palate covered by fibrin.

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secondary syphilis was established. The hearing loss was additionally interpreted as an initial symptom of neurosyphilis. A lumbar puncture was performed, and an analysis of the cerebrospinal fluid (CSF) showed typical lymphocytic pleocytosis (30 cells, 95% mononuclear), altered protein (0.68 g/dL), and a not clearly contributory CSF/serum index with the TPPA negative and the VDRL borderline-positive. As recommended, therapy by administration of intravenous injection of 4 million units of aqueous crystalline penicillin G every 4 hours (24 million units daily) was performed for 14 days. In addition, the patient received a single dose of prednisone 50 mg orally preceding the very first dose of penicillin to prevent the Herxheimer-Jarisch reaction. After he had completed

the 14-day course of intravenous therapy, the patient received additional intramuscular therapy with 2.4 million units of benzathine-penicillin to complete a 3-week course of therapy.

One month after the syphilis had been diagnosed, the patient reported the successful resolution of his symptoms.

CASE 2

A 33-year-old female patient was referred to the Department of Oral Medicine, Dental Radiology and Oral Surgery, Charité, Berlin, by her general dental practitioner for consultation because of unclear changes on her oral mucosa. A smear taken by the

general dental practitioner could not confirm any mycotic infection. Her medical history revealed that about 6 weeks earlier, the patient had noted the formation of vesicles along her upper and lower lip. One week before the first consultation, painful lesions had occurred on the hard palate, left buccal mucosa, and tip of the tongue and at the commissures. Furthermore, the patient had noted skin alterations on her abdomen and in her vaginal area. She assumed that the cause for these symptoms might have been a diet that she had been consuming for 3 months.

On the extraoral clinical examination, multiple erythematous maculae were observed, especially in the area around the navel (Fig 2A). Intraorally, bilateral, slightly whitish papules and erosions were discovered on the hard palate (Fig 2B), oral mucosa of the upper and lower lips (Fig 2C), left commissure (Fig 2D), left lateral tip of the tongue, and attached buccal gingiva in the region of the lower right molars.

During the repeat examination 1 week later, the patient reported that 3 months earlier her husband had

shown similar lesions in the oral cavity. A biopsy performed by his dentist did not reveal any definite specificity. The pathologic changes had healed spontaneously. From the general medical history and considering the occurrence of similar lesions in the patient's husband and the clinical findings, she was referred for serologic testing for syphilis. Initially, the patient rejected the possibility of having developed any sexually transmitted disease. Finally, the diagnosis of secondary syphilis was confirmed by a positive test result (TPPA positive, fluorescent treponemal antibody absorption test [FTA-Abs] positive, and *Treponema pallidum* IgM positive). Subsequently, the patient was treated with intramuscular benzathine-penicillin, with complete symptom remission.

CASE 3

A 42-year-old male patient was referred to the Department of Oral Medicine, Dental Radiology, and Oral Surgery, Charité, Berlin, by his general

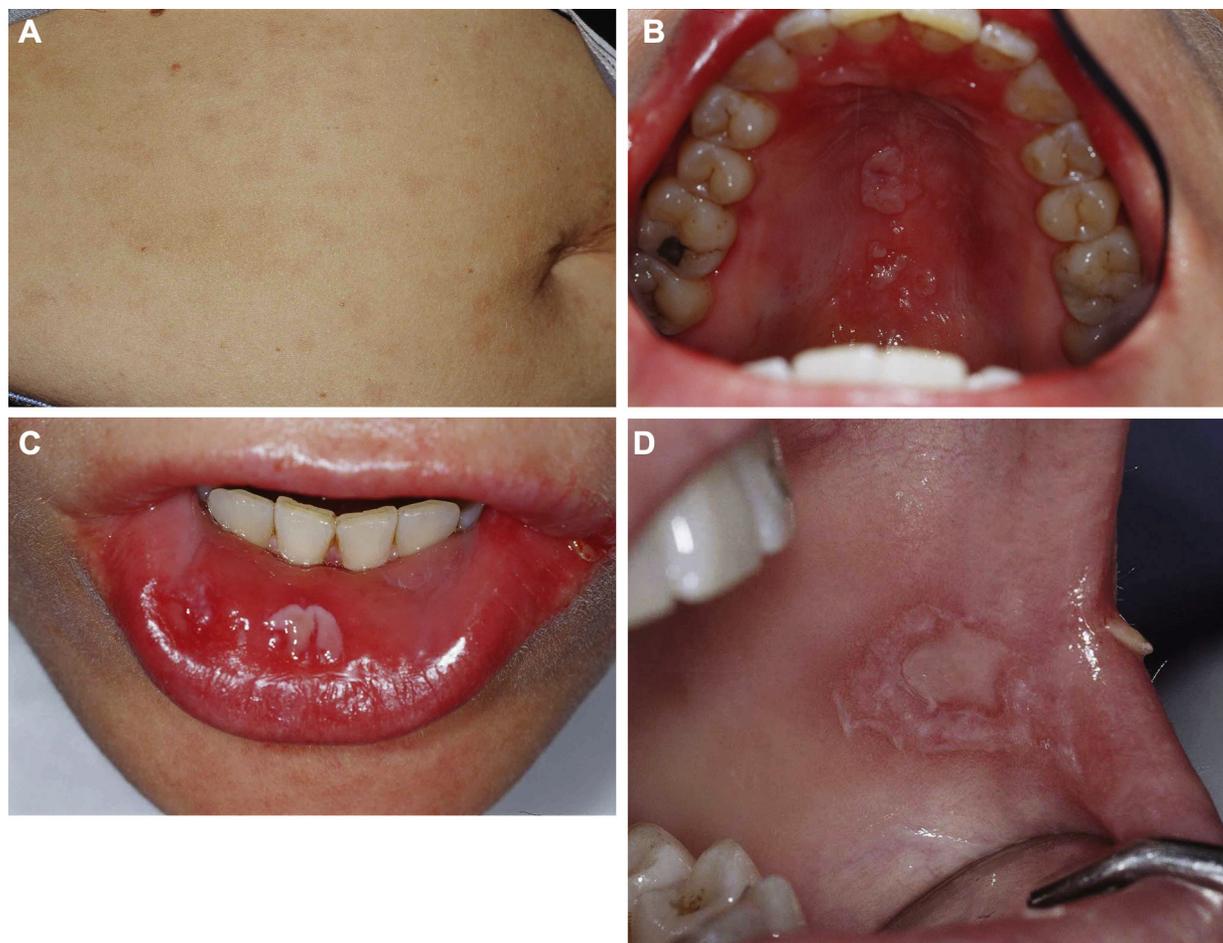


FIGURE 2. Patient 2. A, The area around the umbilicus shows an exanthema with multiple erythematous maculae. B,C,D, Aphthous-like fibrin-covered lesions of the hard palate and lower lip and in the left angle of the mouth related to secondary syphilis.

dental practitioner. The patient had developed slightly painful changes, with adjacent swelling, of the right buccal mucosa. His general medical history was unremarkable.

The patient reported oozing lesions that had occurred at the right commissure after an injury caused by a violent confrontation 4 weeks earlier. Shortly before the emergence of these changes, the patient had been abroad for an extended period.

The intraoral examination revealed a slightly painful ulcer at the right commissure (Fig 3) measuring 10 × 10 mm, accompanied by extraoral swelling of the cheeks and enlarged lymph nodes of the ipsilateral side. The tentative diagnosis was a superinfected major aphthous ulceration. An ointment consisting of topical clobetasol and nystatin was applied, resulting in clinically healed oral mucosa after 2 weeks. However, 3 weeks later, the patient was re-examined. Multiple aphthoid changes of the buccal mucosa and swelling of the local lymph nodes were found. Reddish papules were noted on the palmar surface of the hands



FIGURE 3. Patient 3. Fibrin-covered, indurated ulceration of the right commissure with swelling extending to the buccal mucosa related to primary syphilis.

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and the plantar surface of the feet. Furthermore, an intraoral rash consisting of erythematous maculae on the upper arms and trunk was found. Because of these clinical extra- and intraoral findings, a syphilitic infection was suspected. Serologic testing confirmed the diagnosis of secondary stage syphilis (TPPA positive, VDRL positive, FTA-Abs positive, *Treponema pallidum* IgM positive, C-reactive protein 20 mg/L). Intramuscular administration of benzathine-penicillin led to a disappearance of the exanthema and enanthema after 1 week. Subsequent serologic tests confirmed complete remission 3 months after treatment (VDRL 1:1). The findings at the first examination could retrospectively be diagnosed as a syphilis infection in the first stage.

CASE 4

A 43-year-old male patient was referred to the Department of Oral Medicine, Dental Radiology and Oral Surgery, Charité, Berlin, by a dental practitioner because of lesions of the hard palate that had been present for 2.5 weeks. No remission had occurred after a first topical treatment with a glucocorticoid prescribed by the general practitioner. His general medical history revealed that the patient was HIV positive. For 2 years after the diagnosis, the patient was treated with highly active antiretroviral therapy. At the examination, the patient's CD4+ cell count was 575/μL (normal value, 500 to 1,500/μL), and his viral load was less than the detection limit.

An intraoral enanthema, characterized by multiple erythematous papules with a whitish rim specified as so-called mucous plaques, was discovered. It was observed on the hard palate in the area of the right upper molars, on the upper and lower lips, on the left buccal mucosa, and on the tip of the tongue (Figs 4A,B). His sexual history revealed that the patient was homosexual, with varying sexual partners. From his general medical history and the clinical findings, a secondary stage syphilitic infection was assumed. Consequently, the patient was referred for serologic testing, which revealed a positive result for syphilis (TPPA positive, VDRL positive, FTA-Abs positive, *Treponema pallidum* IgM positive). Therapy with benzathine-penicillin administered intramuscularly led to complete remission of the signs and symptoms.

CASE 5

A 60-year-old female patient with painful oral lesions was referred to the Department of Oral Surgery and Stomatology, University of Bern. Six months previously, she had sought advice at the emergency department of the University Hospital (Inselspital) because of a severe headache. Pansinusitis was suspected, and she was treated with analgesics. Three months

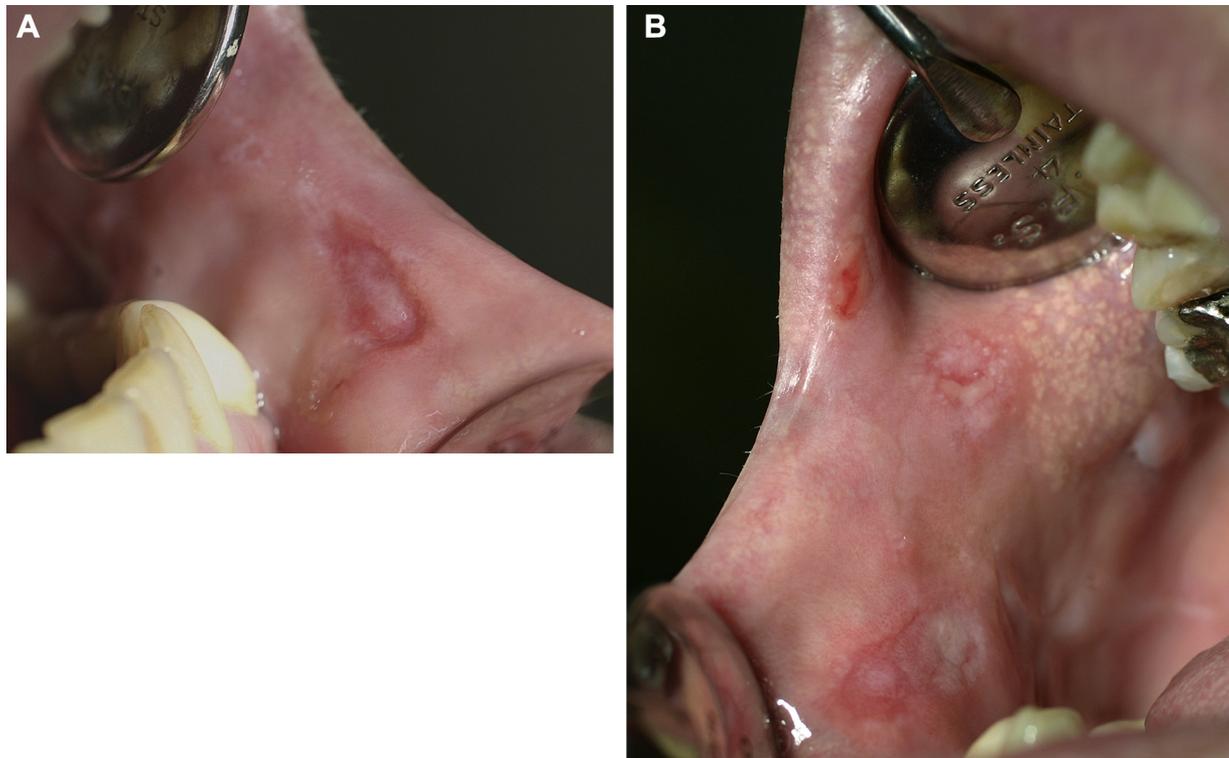


FIGURE 4. A,B, Patient 4. Mucous membrane plaques of the lower lip and buccal mucosa as a manifestation of secondary syphilis.

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later, the patient had developed influenza-like symptoms accompanied by changes of her oral and genital mucosa. A biopsy performed by her gynecologist showed only a lichenoid lesion of the vaginal mucosa.

A clinical examination revealed multiple, partially erythematous papules on the dorsum and the tip of the tongue and bilaterally on the buccal mucosa (Fig 5). An excisional biopsy of the right buccal mucosa was performed, revealing a plasma cell mucositis. Because of the discrepant clinical and pathologic findings and the presence of genital manifestations,



FIGURE 5. Patient 5. Partially erythematous papules on the right posterior dorsum of the tongue related to syphilis.

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serologic testing was performed for syphilis. Because the test results were positive for syphilis (TPPA positive, VDRL positive, FTA-Abs positive) and negative for HIV, the patient was referred to the Department of Infectiology. Additional treatment with azithromycin was administered because she had an allergy to penicillin. Although the clinical and serologic findings did not permit a definitive classification as second or third stage syphilis, the patient refused examination of the CSF. Because the VDRL titer did not decline during the next 2 months, tetracycline was administered, leading to subsequent remission.

Discussion

The presented cases have shown the necessity of including syphilis in the differential diagnosis of unspecific oral ulcerations or erosions and enanthema. In each case, a detailed medical history and clinical examination were of great importance in finding the correct diagnosis.

As reported, the final confirmation always requires serologic testing by an infectious disease specialist, dermatologist, or general medical practitioner. The serologic diagnosis of syphilis consists of the detection of specific and unspecific antibodies. As a screening procedure, the TPPA test is used. Particles sensitized by *Treponema pallidum* antigens cause a positive

agglutination reaction if specific immunoglobulins are present in the patient's serum. Because of the possibility of false-positive results, the FTA-Abs test should be used in the case of positive TPPA results. If present, immunoglobulins against *Treponema pallidum* will be bound and can be detected using fluorescein-coupled antihuman antibodies. To determine the activity of the infection, the quantitative VDRL is used. Bovine cardiolipin is added to the patient's serum, and a positive flocculation reaction indicates the presence of antibodies against supposedly mitochondrial phospholipids from necrotic cells. Therefore, serologic testing for syphilis using VDRL is indirect. Additionally, the enzyme-linked immunosorbent assay and/or Western blot can be used to detect IgM and IgG against *Treponema pallidum*.^{11,12} If involvement of the nervous system is suspected, CSF testing is required. As shown in patients 1, 2, and 5, apart from special techniques such as fluorescence in situ hybridization, regular histopathologic examination of syphilitic lesions can be rather nonspecific. Therefore, the evaluation of biopsies is not of primary importance in cases with a strong suspicion for syphilis.

Treatment depends on the disease stage and is usually penicillin to provide a long-term effect as long as no allergy is known. If the therapy is successful, serologic follow-up monitoring will show a decrease of the VDRL titer. Although penicillin is still highly effective, resistance to second-line antibiotics, especially azithromycin, has been reported.¹³ In addition, considering the coincidence of other sexually transmitted diseases (eg, syphilis and HIV) is important, such as was shown for patient 4.¹⁴

The first stage of syphilis is characterized by the primary complex, including a mostly painless solitary ulceration with a hardened margin combined with ipsilateral lymphadenopathy occurring after an incubation period of 2 to 4 weeks. Representing a local infection, the localization of the lesion will correspond to the site where the bacteria had penetrated the body's epithelial barrier, usually by way of microlesions of the oral or anogenital mucosa. Therefore, extragenital lesions in the primary stage will most frequently be found at anal and oral sites.¹⁵ Primary lesions of syphilis contain large amounts of *treponemae* and are therefore considered to be highly contagious. Such as was seen in patient 3, these lesions will typically heal spontaneously. The differential diagnosis should include major aphthae and/or not otherwise specified ulcers, traumatic lesions, medication-related ulcers, erosive lichen planus, and neoplasia such as oral squamous cell carcinoma and lymphoma.

If the disease is left untreated, up to 90% of patients with primary syphilis will develop a secondary stage.¹⁶ The typical oral manifestations are mucous membrane plaques, such as described in patient 4. Nevertheless,

related lesions can be clinically and histopathologically unspecific, just as was seen in patients 1, 2, and 3, or will mimic other entities. In secondary syphilis, oral manifestations can be present in one third to one half of all patients.¹⁰ Exanthema, especially when affecting the palms of the hands and soles of the feet (such as was seen in patient 4) and accompanying generalized lymphadenopathy, is highly suspicious. Just as are lesions in the primary disease stage, those of secondary syphilis are contagious. Lichen planus, lupus erythematoses, erythroleukoplakia, and candidiasis need to be taken into consideration in the potential differential diagnosis for mucous plaques. Rather nonspecific lesions should be distinguished from minor aphthae, herpes simplex and zoster manifestations, erosive lichen planus, and medication-related ulcers.

About one third of infected patients who do not undergo therapy will have complete spontaneous healing after second stage syphilis; however, two thirds will enter a variable period of latency with an absence of clinical symptoms. In the early phases of latency, defined as a 1-year period after the last exanthema manifestation, the patient should still be considered infectious; this will change in the phase of late latency.¹⁶ One third of untreated patients will develop third stage syphilis, with gummas as characteristic lesions.¹⁶ These oral and extraoral necrotizing foci are not contagious. In industrial countries, because of the highly developed medical system, contact with a patient with syphilis at that stage is unlikely.

As shown in the 5 cases we have presented, the diversity of oral lesions caused by primary or secondary syphilis underlines the importance of taking a thorough medical history from patients with unspecified alterations of the oral mucosa. It should be remembered that syphilis is the great mimicker and should always be included in the potential differential diagnosis in such cases. In particular, the patient's history concerning sexual behavior is crucial. However, it is understandable that patients seeing their dentist are not likely to report details concerning their sexual activities at their first visit.

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