Oral syphilis: report of three cases and characterization of the inflammatory cells

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Abstract

Syphilis is a sexually transmitted infectious disease caused by Treponema pallidum. This study reports 3 cases of syphilis and highlights the importance of identifying oral lesions for its final diagnosis. Case 1: a 48-year-old male patient presented with a bleeding ulcer in the lower lip. Overall clinical examination revealed patchy alopecia and skin target lesions. Case 2: a 61-year-old male patient presented with white spots on the lateral tongue and nodules on the dorsum of the tongue. Overall clinical examination showed erythematous target lesions on the abdomen, forearm, palms of the hand, and soles of the feet. Case 3: a 17-year-old male patient presented with an ulcerated lesion on the tongue and lymph node involvement. The following serologic tests were requested: Venereal Disease Research Laboratory, fluorescent treponemal antibody–absorption, anti–HIV-1 and anti–HIV-2, and anti–hepatitis C Virus. An incisonal biopsy revealed epithelial hyperplasia associated with intense and diffuse mononuclear inflammatory cell infiltration consisting mainly of plasma cells, in a perivascular and perineural distribution. The final diagnosis in the 3 patients was syphilis. Treatment consisted of 1 weekly dose of penicillin (2.4 million units, intramuscular) for 2 or 3 weeks. Immunochemistry reactions for IgM, CD3, CD20, CD68, CD163, S100, CD1a, CD11c, CD83, CD138, and CD208 were performed. Clinicians should be familiarized with oral syphilis lesions in order to be able to diagnose this emerging infectious disease of variable clinical presentation.

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1. Introduction

Syphilis is an infectious disease caused by Treponema pallidum. Transmission of the disease occurs through sexual contact, vertical transmission, or, less frequently, blood transfusions or reused sharp objects [1,2]. Syphilis is an emerging disease, and an increase in the number of cases has been observed in recent years [3].

Syphilis can be divided into different stages: primary, secondary, latent, and tertiary [4]. The first sign of syphilis is a hard chancre, and the lips are the most affected extragenital site [1]. Oral lesions are observed in at least 30% of patients with secondary syphilis and appear as white plaques, papules, or nodules [3]. Involvement of the palms and soles is characteristic of this stage [2]. After the second stage, the disease enters long periods of latency that can last from 10 to 30 years [2,5]. In the third stage, there is involvement of the skin, mucosa, cardiovascular and central nervous systems [2,6], liver, spleen, and other organs [5]. Gingival lesions are characteristic of this stage and may perforate the palate and destroy the nasal septum [2].

The objectives of the present study were to report 3 cases of syphilis with variable clinical characteristics and to highlight the importance of identifying oral lesions for the definitive diagnosis and for establishing adequate therapeutic protocols.

2. Case report

2.1. Case 1

A 48-year-old male patient sought the stomatology outpatient clinic of Universidade Estadual Paulista “Júlio de Mesquita Filho”, São José dos Campos, São Paulo, with a 5-month history of a wound in the lower lip, which spontaneously bleeds at night (Fig. 1A). During anamnesis, the patient reported that he had seen a physician who prescribed Neomycin ointment (30 g, betamethasone valerate + neomycin sulfate, Bunker Indústria Farmacêutica LTDA, São Paulo, Brazil), which did not result in improvement. The patient was submitted to a chest x-ray because of his chronic dry cough, but no pulmonary alterations were detected. The patient reported that he had seen a physician who prescribed Neomycin ointment (30 g, betamethasone valerate + neomycin sulfate, Bunker Indústria Farmacêutica LTDA, São Paulo, Brazil), which did not result in improvement. The patient was submitted to a chest x-ray because of his chronic dry cough, but no pulmonary alterations were detected. The patient was submitted to a chest x-ray because of his chronic dry cough, but no pulmonary alterations were detected. The patient was submitted to a chest x-ray because of his chronic dry cough, but no pulmonary alterations were detected. The patient was submitted to a chest x-ray because of his chronic dry cough, but no pulmonary alterations were detected. The patient was submitted to a chest x-ray because of his chronic dry cough, but no pulmonary alterations were detected.

Case 1: a 48-year-old male patient presented with a bleeding ulcer in the lower lip. Overall clinical examination revealed patchy alopecia and skin target lesions. Case 2: a 61-year-old male patient presented with white spots on the lateral tongue and nodules on the dorsum of the tongue. Overall clinical examination showed erythematous target lesions on the abdomen, forearm, palms of the hand, and soles of the feet. Case 3: a 17-year-old male patient presented with an ulcerated lesion on the tongue and lymph node involvement. The following serologic tests were requested: Venereal Disease Research Laboratory, fluorescent treponemal antibody–absorption, anti–HIV-1 and anti–HIV-2, and anti–hepatitis C Virus. An incisonal biopsy revealed epithelial hyperplasia associated with intense and diffuse mononuclear inflammatory cell infiltration consisting mainly of plasma cells, in a perivascular and perineural distribution. The final diagnosis in the 3 patients was syphilis. Treatment consisted of 1 weekly dose of penicillin (2.4 million units, intramuscular) for 2 or 3 weeks. Immunochemistry reactions for IgM, CD3, CD20, CD68, CD163, S100, CD1a, CD11c, CD83, CD138, and CD208 were performed. Clinicians should be familiarized with oral syphilis lesions in order to be able to diagnose this emerging infectious disease of variable clinical presentation.

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In view of the differential diagnosis of secondary syphilis, a biopsy of the tongue lesion was performed, and the results are shown in Table 1: Venereal Disease Research Laboratory (VDRL), fluorescent treponemal antibody–absorption (FTA-Abs), anti–HIV-1 and anti–HIV-2, and anti–hepatitis C virus (HCV). The clinical and histopathologic findings and serologic tests confirmed the diagnosis of secondary syphilis.

The patient was referred to an infectologist and was treated with 1 weekly dose of penicillin (2.4 million units, intramuscular [IM]) for 3 weeks (Fig. 1F).

2.2. Case 2

A 61-year-old male patient was referred to our service because of a 2-month history of white spots on the tongue. Overall clinical examination revealed red target lesions on the abdomen, soles of the feet, and palms of the hands (Fig. 2A–C). On intraoral examination, nodular-papular lesions measuring approximately 1 cm were observed on the dorsum of the tongue (Fig. 2D) and erythematous lesions on the palate (Fig. 2E). Furthermore, a well-delimited white spot containing a small area of ulceration and showing no painful symptoms was noted on the ventral surface of the tongue (Fig. 2F). During anamnesis, the patient reported self-medication with flucloxacillin (150 mg/wk) for 3 weeks due to a lesion in the genital region, but without improvement.

In view of the differential diagnosis of secondary syphilis, a biopsy of the tongue lesion was performed. Microscopic analysis showed intense epidermal hyperplasia, exocytosis, and intraepithelial microabscesses, in addition to intense perivascular and perineural plasma cell infiltration (Fig. 2G–I). The results of the serologic tests (VDRL, FTA-Abs, anti–HIV, and anti–HCV) showed in Table 1 indicated secondary syphilis. The patient was referred to an infectologist and was treated with 1 weekly dose of penicillin (2.4 million units, IM) for 2 weeks.

2.3. Case 3

A 17-year-old male patient presented with a 2-month history of an ulcer on the lateral border of the tongue. During anamnesis, the patient reported the use of oral mouth rinse and Omnolon A Orabase ointment (trimcinolone acetonide, Bristol-Myers Squibb Farmacêutica SA, Santo Amaro, São Paulo, Brazil), without satisfactory results. Extraoral clinical examination revealed a 4-cm nodule in the upper neck region that was mobile, tender to palpation, and asymptomatic (Fig. 3A). Intraoral examination showed a 3-cm asymptomatic ulcer on the right lateral border of the tongue (Fig. 3B).

The differential clinical diagnoses included neoplastic and infectious diseases. An incisional biopsy of the tongue lesion was performed, and microscopic analysis revealed pseudoeipitheliomatous hyperplasia, exocytosis, and intraepithelial microabscesses (Fig. 3C). Moreover, there was a prominent subepithelial inflammatory infiltrate, as well as evident perivascular and perineural plasma cell infiltration (Fig. 3D). The final diagnosis of syphilis was made based on the serologic tests (VDRL, FTA-Abs, anti–HIV, and anti–HCV) whose results are summarized in Table 1. The patient was referred to an infectologist and treated with 1 weekly dose of penicillin (2.4 million units, IM) for 2 weeks.

3. Immunohistochemical analysis

All tissue specimens were fixed in 10% neutral-buffered formalin for 24 hours at room temperature, embedded in paraffin at 55°C, and cut into consecutive parallel 3-μm-thick sections. For immunohistochemistry, the slides were hydrated and treated with hydrogen peroxide.

For retrieval of the XIIIa, CD3, CD20, CD68, CD163, S100, CD1a, CD11c, CD83, CD138, and CD208 epitopes, the tissue specimens were pretreated with 10 mM sodium citrate buffer, pH 6.0, in a pressure cooker. The CD123, CD303, and CD207 epitopes were masked by pressure cooker pretreatment in 10 mM Tris/1 mM EDTA buffer, pH 9.0. The sections were then successively incubated with the primary antibodies (Table 2). Next, the sections were incubated with the secondary antibodies conjugated with streptavidin–biotin–peroxidase (K0690; Universal Dako LSAB + Kit, Peroxidase, Carpinteria, California). The reactions were then successively incubated with the primary antibodies (Table 2).
were developed with diaminobenzidine, and the sections were counterstained with Carazzi hematoxylin.

A larger number of CD3+ cells than CD20+ cells were observed in the lesions. CD138 staining revealed numerous plasma cells, highlighting their perivascular and perineural distribution pattern. The percentage of CD68+ and CD163+ cells was similar and the staining pattern was diffuse, suggesting an M2-macrophage phenotype. However, no organized granulomas were observed. Dendritic cell (DC) markers revealed numerous XIlla+ and S100+ cells, and CD11c+ cells, followed by CD1a+ and CD207+ cells. CD123+ and CD303+ cells were scarce; however, these latter presented in lesser number. Similarly, mature DCs highlighted by CD83 and CD208 markers were scanty (Fig. 4A–L). Except S100 and CD1a and CD207, all other DC markers showed preferential connective tissue location.

4. Discussion

Syphilis is currently considered an emerging disease [4], which is mainly acquired through sexual contact with an infected lesion [3].
Fig. 4. Immunohistochemical results. (A) Numerous CD3-positive cells, especially in the subepithelial region (diaminobenzidine [DAB], magnification ×200). (B) Few CD20-positive cells (DAB, magnification ×200). (C) Diffuse CD68 immunoreexpression (DAB, magnification ×200). (D) Diffuse pattern of CD163-positive cells (DAB, magnification ×200). (E) CD138 immunoexpression in numerous inflammatory cells with dendritic morphology (DAB, magnification ×200). (F) Few CD1a-positive cells in the epithelium (DAB, magnification ×200). (G) Numerous XIIIa-positive cells in a subepithelial location (DAB, magnification ×200). (H) Scarce CD208-positive cells (DAB, magnification ×400). (I) CD11c immunoreexpression highlighting plasma cells and the hyperplastic squamous epithelium. (DAB, magnification ×200). (J) In the connective tissue, scarce CD303-positive cells were observed (DAB, magnification ×200). (K) CD123-positive cells were more numerous than the CD303-positive cells (DAB, magnification ×200). (L) At a deeper level, CD138 highlighted numerous plasma cells surrounding skeletal muscle fibers (DAB, magnification ×200).

Table 2

<table>
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The sex industry, promiscuous behavior, a reduction in the use of condoms, and the practice of oral sex have caused the increase in cases [2,5,7], especially among young patients, a group in which sexually transmitted diseases are more common [8]. However, 2 of the cases reported here were married adult men who reported extramarital sexual relations with different women and who refused to inform their partners about the disease. This fact favors the dissemination of the disease and delays the diagnosis and treatment for infected individuals. Men are 14 times more affected than women [7]. Of these, 83.9% are men who have had homosexual relations [9], such as case 3 who was a homosexual adolescent boy. In the case of this group and of heterosexuals, the interaction between HIV infection and syphilis is of great clinical and epidemiologic interest [5]. In the present study, the HIV test results were negative. However, case 1 was infected with HCV, in contrast to the findings of Price et al. [10].

Clinically, primary syphilis is characterized by the presence of a hard chancre, which is an asymptomatic ulcerated lesion with indurated margins [1,8]. The lesions are generally solitary [3,11] and rarely occur in the mouth [4], but if present, the lips are the most affected site [3]. An association with painless regional lymphadenopathy has been reported [1,8]. Primary chancres heal spontaneously within 4 to 5 weeks without leaving scars [1,2,8]. Extragential chancres appear in 5% to 14% of cases; two-thirds of these cases occur in the mouth or perioral region after unprotected oral sex [12], as reported by patient 3.

An expressive and rapid increase in the number of disease-causing microorganisms and, consequently, in the clinical manifestations is observed in secondary syphilis [2]. In the skin, the lesions can be symmetrical and appear as rose-colored patches in 75% of patients [1]. The syphilitic roseola is the first clinical sign of secondary syphilis [12], and involvement of the palms of the hands and soles of the feet is characteristic [2]. Some patients present with diffuse or marked alopecia in the temporoparietal and occipital region, known as patchy alopecia [2,11]. In the present study, patients 1 and 2 had multiple skin lesions, although case 1 exhibited no erythematous spots in the palms or soles, only case 2. The loss of hair and eyebrows [12] was observed in patient 1, a finding seen in only 5% to 6% of affected patients [5].

Oral lesions of secondary syphilis are typically multiple and symptomatic [2,8,13]. Lesions in the upper lip are more common in men, whereas those in the lower lip are more common in women [3]. Patient 1 had a single lesion in the lower lip. Secondary syphilis lesions can appear as multiple mucosal spots surrounded by erythema on the soft palate, tongue, and oral mucosa [1]. Nodular lesions on the tongue are uncommon [3]. However, case 2 presented with multiple papular-nodular lesions on the tongue, an ulcerated lesion on the ventral surface of the tongue, and erythematous areas on the palate. All cases reported here exhibited variable clinical characteristics, a fact that makes the final diagnosis of syphilis difficult.

There is a broad spectrum of differential diagnoses of syphilis due to the variable clinical manifestation of the disease [4]. When affecting the lip, syphilis lesions can simulate squamous cell carcinoma [3]. Erythema multiforme affects the mucosa and skin, and its most marked characteristics are target-shaped erythematous rings on the palms and soles and ulceration with crusting on the lip [14]. For these reasons, the clinical diagnosis in case 1 was erythema multiforme, although the patient did not report the use of drugs, episodes of herpes simples, or food allergy.

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The diagnosis of syphilis is generally based on clinical, microscopic, and serologic findings. The last is essential because the clinical and microscopic findings are variable and relatively nonspecific [5]. Considering only microscopic features, the intense subepithelial plasma cell infiltration frequently observed in syphilis should be differentiated from idiopathic plasmacytosis, IgG4-related sclerosing disease, contact stomatitis, candidiasis, inflammatory pseudotumor, and plasmacytoma [15]. Primary and secondary syphilis is characterized by plasma cell infiltration which extends deeply beyond the lamina propria and around capillaries and nerve bundles [5]. In the lamina propria, plasma cells, together with lymphocytes and macrophages, arrange themselves in a band-like pattern (lichenoid infiltration) [5]. Tertiary oral syphilis is characterized by pseudoepitheliomatous hyperplasia and granulomatous inflammation with a central zone of acellular necrosis, accompanied by histiocytes and multinucleated giant cells. Obliterating endarteritis is observed in all stages of the disease [5]. In the present study, histochenical staining with Warthin-Starry stain was performed and no structures compatible with spirochetes were detected. The presence of bacterial colonies in oral mucosal biopsies [12] impairs the interpretation of the results of Warthin-Starry staining, thus limiting its use. In addition, the sensitivity of this method is 41% when biopsies are evaluated. Immunohistochemistry shows a higher sensitivity (71%) than Warthin-Starry staining (41%) for the assessment of secondary syphilis lesions.

In the present study, we evaluated the immunohistochemical profile of the inflammatory cell infiltrate using a broad panel of antibodies. The results showed a larger number of T cells than B cells, whereas numerous plasma cells were observed in a subepithelial location and in the deeper connective tissue compartments. No evident granuloma formation was noted; however, the observation of diffuse CD68/CD163 staining in the biopsy samples suggests an M2-macrophage phenotype. The classically activated M1-macrophages (HLA-DR+/CD68+) are highly aggressive against bacteria and produce large amounts of pro-inflammatory cytokines. The alternatively activated anti-inflammatory M2-macrophages (CD68+/CD163+) exert different functions, such as the regulation of immunity, maintenance of tolerance, and tissue repair [16]. Moreover, plasmacytoid DCs were scarce in the connective tissue, and the larger number of CD123+ cells compared with CD303+ cells indicates a mature phenotype of plasmacytoid DCs. Finally, the detection of a larger number of S100+, Xllla+ and CD11c+ cells, followed by CD1a+ and CD207+ cells (all of them immature DC markers), compared with CD83+ and CD208+ cells (which are mature DC markers), in the biopsy samples suggests functional abnormalities of DCs in patients with syphilis, a fact that might be of importance for the understanding of immune dysregulation in this disease [17].

There are 2 nonspecific (nontreponemal) serologic tests for the diagnosis of syphilis: VDRL [11,12] and rapid plasma reagin [1,11,12]. If the results of these tests are positive, more specific (antitreponemal) tests are used for confirmation [1]: FTA-Abs [12], microhemagglutination assay for T pallidum antibodies, and T pallidum particle agglutination assay [12]. In the present study, all cases were tested positive in the VDRL and FTA-Abs assays. The 2 tests were requested at the same time because of their accessible cost and rapid execution and because of the strong clinical suspicion of syphilis, especially in case 2.

Syphilis is a disease with devastating effects if untreated [11]. Although effective and low-cost treatment is available, syphilis continues to be a public health problem [2]. Penicillin [18] is effective at any stage, with the regression of primary and secondary lesions after a single application [1]. In the present study, the efficacy of this drug was demonstrated by the administration of a weekly dose of 2.4 million units (IM) and the observation of complete remission of the lesions after the first dose. However, the patients should be followed up by serologic testing at 6 and 12 months posttreatment [11].

Syphilis has important implications for clinicians because manifestations can occur in the mouth and perioral region and primary and secondary lesions are highly contagious. Furthermore, the variable clinical presentation of syphilis can delay the diagnosis and treatment, favoring dissemination of the disease. For these reasons, dentists should get familiarized with the clinical manifestations of syphilis. In view of the increase in the number of syphilis cases, awareness and prevention campaigns should be implemented.

Authors’ contributions

Luciana Rocha Strieder and Estela Kaminagakura were involved in clinical attendance and drafting the manuscript. Jorge Esquiche León performed the microscopic and immunohistochemical analyses. Yasmin Rodarte Carvalho performed the microscopic analyses. The final version was revised and approved by all the authors.

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