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Acquired oral syphilis: A multicenter study of 339 patients from South America

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Abstract

Objective: To report the clinicopathologic features of acquired oral syphilis cases in South American countries.

Materials and Methods: Clinical data were retrospectively collected from the records of 18 oral diagnostic services in Argentina, Brazil, Chile, Colombia, Venezuela, Uruguay, and Peru. Serologies of nontreponemal and treponemal tests were used for diagnosis.

Results: The series comprised 339 cases of acquired oral syphilis. Secondary syphilis ranked as the most common stage (86.7%). Lesions were more frequent among males (58.0%) and young adults with a mean age of 33.3 years. Individuals aged 20–29 years were most affected (35.3%). The most commonly involved sites were the tongue (31.6%), lip/labial commissure (25.1%), and hard/soft palate (20.4%). Clinically, acquired oral syphilis usually presented as mucous patches (28.4%), papules (25.7%), and ulcers (18.1%). Skin manifestations occurred in 67.7% of individuals, while lymphadenopathy and fever were observed in 61.3% and 11.6% of all subjects, respectively. Most patients were treated with the benzathine penicillin G antibiotic.

Conclusion: This report validates the spread of acquired oral syphilis infection among young adults in South America. Our directives include accessible diagnostic tools for proper disease screening, surveillance, and counselling of affected individuals, especially in low- and middle-income countries.

KEYWORDS
acquired syphilis, oral mucosa, public health, sexually transmitted infections, syphilis, *Treponema pallidum*

1 | INTRODUCTION

Syphilis is a bacterial infection caused by *Treponema pallidum*, first described in the late 15th century (Ghanem et al., 2020). It is considered to be one of the most common sexually transmitted infections (STI) worldwide, with about 6 million new cases each year among adolescents and adults (Newman et al., 2015). The prevalence rates have varied and have increased considerably across different nations and populations in the last decades (Kenyon et al., 2016; Schmidt et al., 2019). The lowest estimated prevalence in high-income countries is 0.2%, while in middle and low-income economies, it ranges from 0.3% to 1.3% (Kitayama et al., 2017). Evidence demonstrated that rates across the world have declined since the advent of penicillin. However, in countries of Sub-Saharan Africa, the incidence has persisted at very high levels compared to other locations (Kenyon et al., 2016). In Latin America, chronological trends have revealed that syphilis has become well settled in some metropolitan areas of Brazil and Argentina and highly prevalent in other large cities (Zoni et al., 2013).

Syphilis can be considered congenital or acquired. The former occurs through mother to child transmission. The latter is transmitted by blood transfusion or sexual contact (Forrestel et al., 2020). Depending on the time elapsed after exposure to the bacteria, acquired syphilis is categorized as primary, secondary, early nonprimary nonsecondary, and late or unknown duration syphilis (Forrestel et al., 2020). The clinical manifestations of syphilis are

protean and can mimic other diseases, usually showing mucocutaneous involvement, including lesions in the oral cavity (de Arruda et al., 2021; Forrestel et al., 2020; Lampros et al., 2021; Matias et al., 2020; Schuch et al., 2019; Smith et al., 2021; Thums et al., 2021). Nevertheless, diagnosing acquired syphilis through oral manifestations can be difficult and can lead to misdiagnosis or underdiagnosis (de Arruda et al., 2021; Schuch et al., 2019). Considering that the number of documented positive syphilis cases may be underestimated, about 500 cases of acquired oral syphilis (AOS) have been described in the literature (Lampros et al., 2021; Matias et al., 2020; Schuch et al., 2019; Smith et al., 2021; Thums et al., 2021). Although the largest number of reported cases of AOS came from North and South America (Matias et al., 2020; Schuch et al., 2019; Thums et al., 2021), collaborative studies are still very scarce.

It is difficult to estimate the global burden of syphilis precisely because of the frequently asymptomatic nature of the infection, the absence of reliable and accessible diagnostic tools impairing adequate screening and poor surveillance in many countries, as well as issues regarding notification (Adawiyah et al., 2021; Korenromp et al., 2019; Schuch et al., 2019). If syphilis is not fully addressed, this disease can increase vulnerability to HIV, lead to pregnancy complications, and have an impact on the spread of the chain of STI (Adawiyah et al., 2021; Korenromp et al., 2018, 2019). Since acquired syphilis indeed requires attention in terms of public health policies and diagnostic strategies, epidemiological studies gathering data from referral services provide more accurate information for these goals.

In the present study, we report cases of AOS diagnosed at 18 referral services in seven South American countries. As far as we know, this is the first multicenter study documenting cases of AOS in Argentina, Brazil, Chile, Colombia, Venezuela, Uruguay, and Peru. The study also provides a discussion of clinical and demographic data, as well as the management of the disease globally.

2 | MATERIALS AND METHODS

2.1 | Study design, participating countries, and ethical issues

This multicenter retrospective study was conducted in seven South American countries. Cases of AOS were obtained from a consortium of 18 referral services of oral diagnosis in Brazil (Universidade Federal do Rio de Janeiro, Universidade do Estado do Rio de Janeiro, and Universidade Federal Fluminense, Rio de Janeiro; Universidade Federal de Minas Gerais and Pontifícia Universidade Católica de Minas Gerais, Belo Horizonte; Universidade Estadual de Campinas, Piracicaba; Universidade Federal do Pará, Belém; Private Pathology Laboratory, Aracaju), Argentina (Universidad Nacional de Córdoba, Córdoba; Hospital Señor del Milagro, Salta; and Hospital Alemán, Buenos Aires), Chile (Universidad Mayor and Universidad Andrés Bello, Santiago; Universidad de Valparaíso, Valparaíso), Colombia (Universidad de Cartagena, Cartagena), Venezuela (Universidad Central de Venezuela, Caracas), Uruguay (Universidad de la República, Montevideo), and Peru (Universidad Peruana Cayetano Heredia, Lima). This study was approved by the local Ethics Committee (#10723019.0.1001.514). Patient anonymity was ensured in accordance with the Declaration of Helsinki.

2.2 | Sample

Data collection took place in December 2020. Data were extracted from information provided by the clinician in the referral services on patients' records as follows: data about the affected individuals such as sex, age, risk factors for STI (drug users, multiple partners, sex workers, and whether the patient was a man who had sex with men [MSM]), and human immunodeficiency virus (HIV) status. The characteristics of the oral lesions were described in terms of anatomical location (buccal mucosa, floor of the mouth, gingiva/alveolar ridge, hard/soft palate, lip/labial commissure, oropharynx/tonsil/uvula, tongue, and vestibule), stage of the disease (primary, secondary, early nonprimary nonsecondary, and late or unknown duration syphilis) (Forrestel et al., 2020), clinical aspects, and clinical differential diagnosis. The latter was categorized into infectious diseases, potentially malignant oral disorders, malignant neoplasms, immune-mediated diseases, and others. When available, data on manifestations on the skin, relevant medical history (fever and lymphadenopathy), and treatment provided were also recorded.

2.3 | Diagnostic rendering

Syphilis was diagnosed based on the criteria of the Centers for Disease Control and Prevention, which include significant clinical features such as localized or diffuse mucocutaneous lesions associated with double-positive serological results of a treponemal assay (*T. pallidum* particle agglutination assay [TP-PA], fluorescent treponemal antibody absorption [FTA abs], enzyme immunoassay [EIA], and a nontreponemal assay, the venereal disease research laboratory [VDRL] test; or the rapid plasma reagin [RPR] test) (Centers for Disease Control & Prevention, 2015).

Microscopic evaluation of hematoxylin and eosin-stained slides and immunohistochemical analysis for the detection of *T. pallidum* were available in some cases, as serological confirmation of syphilis may have been preceded an oral biopsy in order to rule out other conditions. Records without specific information on the diagnosis of syphilis were excluded.

2.4 | Data analysis

Descriptive and quantitative data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software, version 25.0 (SPSS Inc., Armonk, NY, USA).

3 | RESULTS

3.1 | General information and population characteristics

A total of 339 cases of AOS were included in the study. Figure 1 illustrates the distribution of cases in South America. Summarized and detailed information about the cases of each country is reported in Tables S1 and S2, respectively. Argentina (44.5%) and Brazil (40.7%) were the countries with the highest number of AOS cases. The survey was conducted on 196 (58.0%) male and 142 (42.0%) female individuals. The male-to-female ratio was 1.4:1. Mean age was 33.3 ± 13.4 years (range: 8–86 years), and the age group most represented was that of individuals between 20 and 29 years (35.3%). The majority of AOS lesions occurred in one anatomical location (56.8%). Tongue (31.6%), lip/labial commissure (25.1%), and hard/soft palate (20.4%) were the sites most commonly affected. The diagnosis of secondary syphilis was established in 86.7% (n = 281) of the cases, followed by the primary stage in 12% (n = 39), and unknown duration or late stage (tertiary) in 0.9% (n = 3) of the cases. One case was of an early nonprimary nonsecondary syphilis (0.3%).

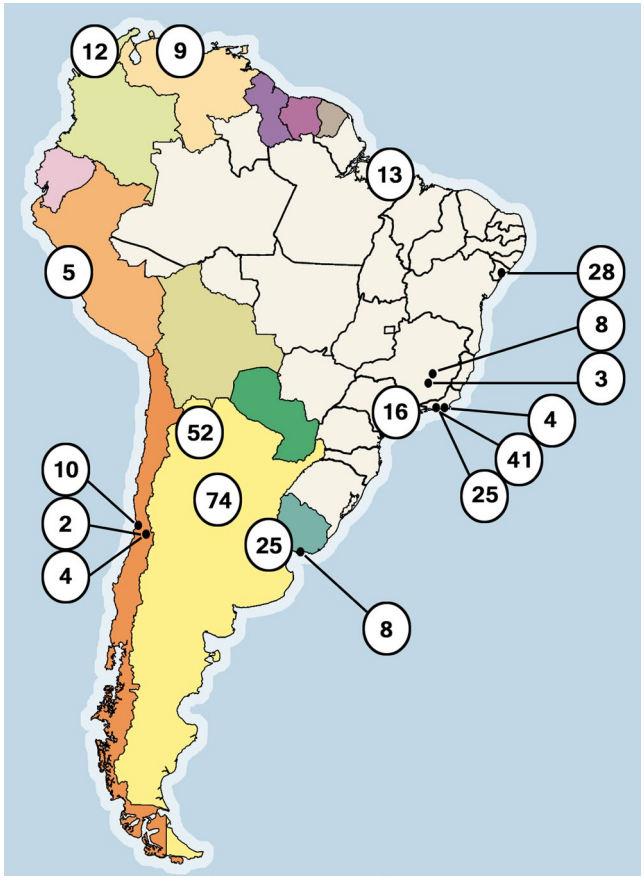

FIGURE 1 An overview of the distribution of cases of acquired oral syphilis across South America (n = 339)

3.2 | Clinical features of primary syphilis

In 33/38 cases of primary syphilis, one anatomical site (86.8%) was involved. In one case, information on anatomical location was unavailable. The lip/labial commissure (41.5%) and tongue (30.2%) were the main affected locations (Figure 2). The most common clinical presentation of the primary stage was an ulcer (chancre) (n = 27/38; 71.0%). While 15/18 (83.3%) of the affected individuals revealed lymphadenopathy and 1/10 (10%) had fever, no one had cutaneous manifestations.

3.3 | Clinical features of secondary syphilis

Regarding cases of secondary syphilis, 50.5% (n = 142) affected one site, followed by 21.0% (n = 59) affecting two sites, and 20.3% (n = 57) and 8.2% (n = 23) of cases affecting three or more sites. The tongue (31.0%) was the most commonly affected site, followed by lip/labial commissure (23.6%), and hard/soft palate (21.7%) (Figure 3). Clinically, secondary syphilis presented mainly as mucous patches (31.5%), papules (27.6%), and/or reddish spots (15.4%). Cutaneous manifestations were observed in 61/181 (33.7%) of the individuals (Figure 4). Lymphadenopathy was observed in 119/200 (59.5%) of the patients, while 110/114 (96.5%) subjects did not develop fever.

3.4 | Clinical features of unknown duration or late (tertiary) syphilis

All three (0.9%) cases affected male individuals who were 35, 55, and 57 years old. Two cases presented as gumma affecting the dorsum of the tongue, while one case involved the palate and neighboring regions. Clinically, the latter case exhibited palate perforation and involvement of the nasal cavity (Figure 5). No individual had been infected with HIV. Tuberculosis and malignant neoplasms were listed as differential diagnoses for the lesions affecting the tongue, while lymphoma, leishmaniasis, and cocaine induction were considered for palatal bone perforation.

3.5 | Differential diagnosis and microscopic findings

Oral biopsies followed by microscopic analysis were performed in 114/290 cases (39.3%) (Table S1) under a wide list of clinical diagnostic hypotheses, including infectious diseases (38.6%), oral potentially malignant disorders (14.0%), malignant neoplasms (12.1%), and immune-mediated diseases (10.1%) (Table S3). Histological sections revealed subepithelial and perivascular lymphoid infiltrate composed predominantly by plasma cells in a connective tissue covered by hyperplastic to ulcerated oral epithelium with marked inflammatory exocytosis. *T. pallidum* was detected by immunohistochemistry in nine cases (Figure 6).

FIGURE 2 Clinical aspects of the primary stage of acquired oral syphilis. (a) Syphilitic chancre as a solitary ulcer with a red base and irregular raised borders in the lateral border and dorsum of the tongue. (b) Single ulcerated lesion with base infiltration and hardened high margins in the mandibular alveolar mucosae. (c) Single erythematous ulcer with base infiltration and greyish-white color in the right upper lip

3.6 | Associated factors and treatment

Seventy-four patients (21.8%) reported factors associated with sexually transmitted syphilis. Most of them reported having had unprotected sex/oral sex (67.6%), multiple partners (17.6%), drug use (9.4%), MSM (2.7%), and being sex workers (2.7%). Information regarding HIV status was available for 224 individuals; of these, 44 (19.6%) were HIV positive. Most patients were treated with benzathine penicillin G (n = 113/119; 97.4%). Three patients received doxycycline due to a history of penicillin allergy (Table S1).

4 | DISCUSSION

Syphilis has had a substantial impact on several at-risk populations over time. Studies have shown an expansion of acquired syphilis globally, including increased numbers in Latin America (Kenyon et al., 2016; Marques Dos Santos et al., 2020; Newman et al., 2015; Zoni et al., 2013). In Brazil, upward trends in the frequency of syphilis have been observed in all municipalities and in the five macroregions between 2007 and 2017 (Marques Dos Santos et al., 2020). In China, an annual percentage change of 16.3% was estimated for syphilis from 2004 to 2013 (Yang et al., 2017). Conversely, in the United Kingdom, there was an increase in the diagnosis of syphilis among MSM and a decrease among non-MSM and women (Mohammed et al., 2016). This study reports the larger series of AOS cases from South America to date, with most patients being represented by young adult men with oral manifestations of syphilis in the secondary stage at the time of diagnosis. The results are in line with previous studies (Lampros et al., 2021; Leuci et al., 2013; Matias et al., 2020; Schuch et al., 2019; Smith et al., 2021; Thums et al., 2021). The findings were also consistent across a broad spectrum of manifestations of oral syphilis, particularly in secondary-stage infections, mimicking a variety of other diseases that affect the oral cavity (de Arruda et al., 2021; Lampros et al., 2021; Schuch et al., 2019).

Herein, individuals of all age groups were infected with AOS. However, about 60% of cases occurred in patients in the third and fourth decades of life, as also previously reported (Schuch et al., 2019; Thums et al., 2021). Interestingly, adolescents were equally affected in terms of the number of cases compared with individuals in their 40s and 50s. In part, sexual initiation occurring in adolescence may reasonably explain this finding, as a recent study demonstrated that age (16–25 years), lower socioeconomic class, smoking habit, not wearing a condom during the first sexual intercourse, and having had a same-sex sexual experience were associated with syphilis (Kops et al., 2019). Unfortunately, an isolated case of an 8-year-old boy was registered in one of the services. According to Long (2020), the vast majority of AOS cases in pediatric patients are caused by sexual transmission, in situations that arise as a result of sexual abuse or aggression by an infected adult against a young individual, mainly in underprivileged areas. In this respect, it is difficult, particularly for oral health practitioners, to notify legal authorities about child sexual abuse, unless there is irrefutable evidence to support the claim. Thus, these remarks suggest that strict measures should be taken to raise social awareness of this issue among children, their parents, and caregivers (Long, 2020).

Since 2000, the increase in the rates of primary and secondary syphilis in the United States has been largely related to a rise in rates among men (Schmidt et al., 2019). Although in the current study, men were slightly more affected than women, a French series revealed a marked predilection for men, representing 95% of the survey (Lampros et al., 2021). Likewise, in a recent report by Smith and collaborators (2021), only one of the 19 individuals affected by AOS was a woman. Another study stressed that affected males are older than females (Thums et al., 2021); however, the data reported herein contrast with all of these findings. Interestingly, when analyzing data from Argentina and Brazil, countries with the highest rates of AOS, men ranked first among affected individuals. We believe that all the circumstances mentioned above may be the reasons why men are more affected than women. However, what also draws attention in

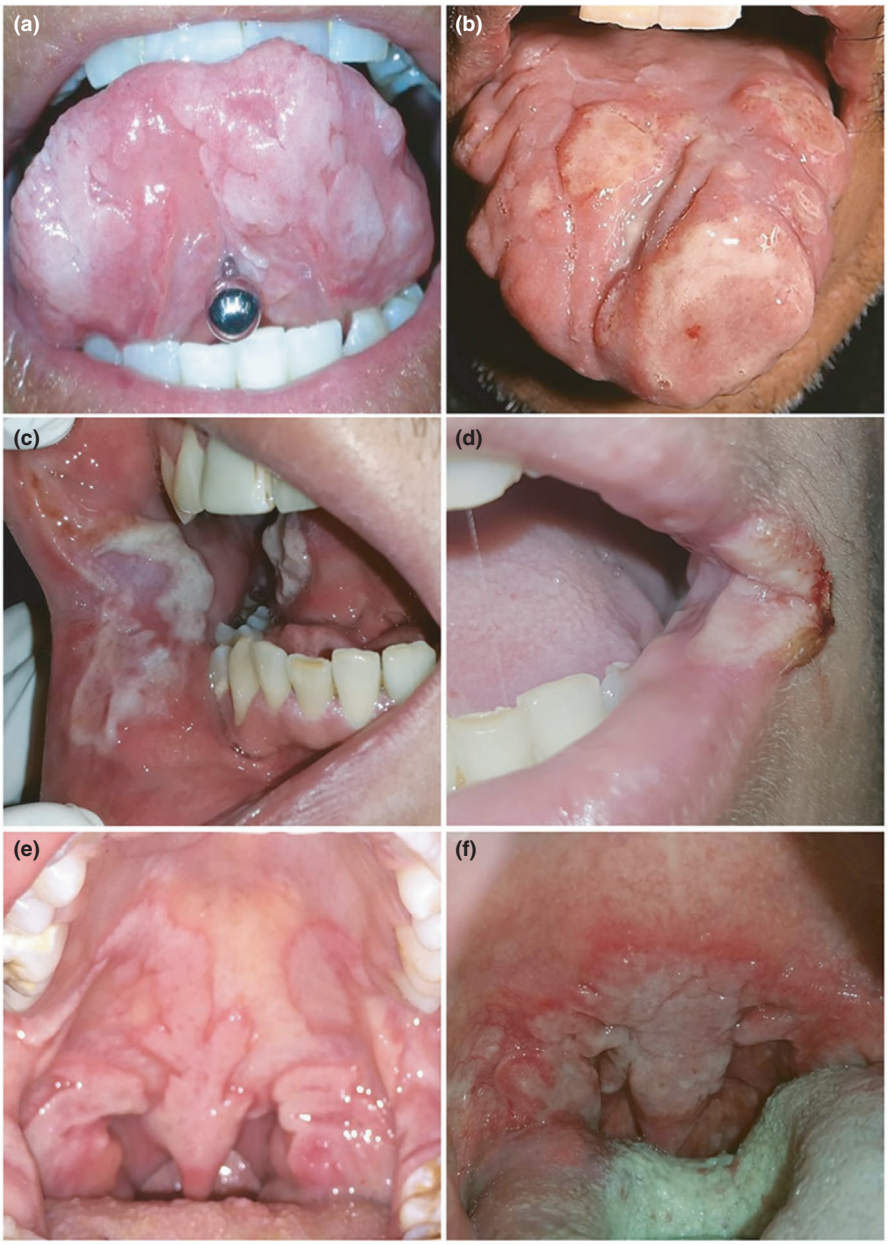

FIGURE 3 Clinical aspects of the secondary stage of acquired oral syphilis. (a) Irregular mucous patches exhibiting a greyish-white color covering the ventrum of the tongue. (b) Exuberant mucous patches covering the dorsum and the lateral border of the tongue. Lesions showing yellowish-white and reddish ulcers of different sizes. (c) Extensive mucous patches with erythematous areas in the region of the right labial commissure and buccal mucosa showing greyish-white and reddish ulcers. (d) In the left labial commissure region, note the presence of mucous patches exhibiting yellowish-white and reddish ulcers with a fibrinous pseudomembrane. (e) Extensive irregular mucous patches of greyish-white color surrounded by a reddish halo in the retromolar region, buccal mucosa, soft palate, uvula, and tonsils. Note that the adjacent patches fuse and a sinuous appearance resembling a "snail-track is formed". (f) In the soft palate, uvula, and tonsils, note the irregular and extensive mucous patches of greyish-white and reddish color with surrounding erythematous areas

this scenario is the trend of affected women. Of note, the number of cases of syphilis among Brazilian women aged 15–49 years is proportionately higher than the global prevalence (Barbosa et al., 2021). Linked to this, socioeconomic variables such as low levels of schooling were frequent in this population, as also reported in Argentina, China, and the United States (Barbosa et al., 2021; Korenromp et al., 2018). Nonetheless, cultural influence should not be ruled out, since regions in South America still have taboos about women's sexual activity and routine screening as well as stigmas attached to their reproductive health (Chandra-Mouli et al., 2019).

Trends and increases in syphilis, in particular AOS, are associated with different factors, but the underlying determinants of infection continue to be unprotected oral sex, multiple sexual partners, MSM, and HIV co-infection (Kenyon et al., 2016; Schmidt et al., 2019; Zoni et al., 2013). These findings are contemporary and represent a substantial burden on the health and well-being of young adults (Forrestel et al., 2020). Evidence indicates that MSM are disproportionately affected by syphilis, with a significant number of cases diagnosed in recent years (Schmidt et al., 2019; Solomon & Mayer, 2015). However, in the present study, this issue sparks off an interesting debate. First, the vast majority of individuals did not report whether there had been any risk factor associated with the infection. In Brazil, for example, the prevalence of self-reported discrimination against young MSM adults is high and can influence vulnerability to HIV, increasing exposure to risky sexual behaviors (Magno et al., 2019). Second, the figures of positive cases of syphilis can be underestimated, as the number of nonshows at services to obtain the results of the requested tests is high (Schuch et al., 2019). Although European countries have used partner notification as one of a series of measures to control STI since the early 1900s (Lowndes et al., 2004), in South America, compulsory notification has only been applied to acquired syphilis very recently, with government regulations

FIGURE 4 Clinical aspects of the secondary stage of acquired syphilis. (a) Irregular erythematous plaque in the palate. (b) Regression of the lesion with the benzathine penicillin G antibiotic treatment. (c, d) In palmoplantar involvement, note erythematous-brownish papules and plaques surrounded by a desquamation collarette (Biett's collar)

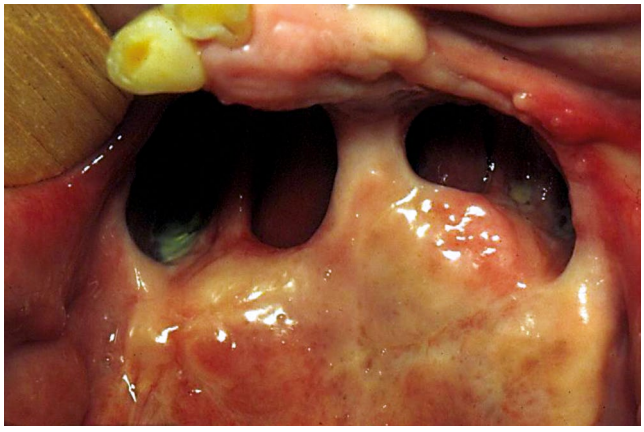

FIGURE 5 Clinical aspects of unknown duration or late (tertiary) syphilis. A 35-year-old man with asymptomatic anterior palatal perforation. He was diagnosed with syphilis at the age of 17

set in place in Peru in 2009, in Brazil in 2010, and in Uruguay in 2013 (Cabrera et al., 2019; Marques Dos Santos et al., 2020). Yet, mandatory syphilis notifications in other countries of this continent are still deficient (Zoni et al., 2013). This certainly implies a scarcity of screening for other STI, leading to inaccurate information about HIV-infected individuals, for instance (Schuch et al., 2019). On the other hand, it is speculated that the low frequency of HIV patients in AOS studies can be attributed to the fact that these individuals are monitored by an infectious disease physician, who is quite likely to diagnose syphilis in the early stages (Thums et al., 2021).

In this study, about 90% of individuals with AOS were in the secondary stage of the disease. Oral manifestations of secondary syphilis are typically painful and multiple and can be accompanied by skin eruptions. The duration of signs and symptoms varies from 4 to 10 weeks (de Arruda et al., 2021; Little, 2005). Herein, the most common oral lesions observed were mucous patches, papules, or ulcers. Isolated or multiple sites were involved, including the tongue, lip, and labial commissure, as well as the palate, as also observed in a previous study (Schuch et al., 2019). Moreover, coexisting lesions in the oral cavity and neighboring regions with clinical signs of lymphadenopathy were detected in the individuals of this series. Indeed, syphilitic lymphadenitis is still a relevant differential diagnosis of cervical lymphadenopathy, through rarely clinically suspected (Ikenberg et al., 2010).

Data on 39 individuals with primary syphilis were also provided in the current study. Overall, typical oral lesions taking place at this stage were ulcerated and single (chancre), with base infiltration and hardened high margins associated with a low frequency of lymphadenopathy and the absence of cutaneous manifestations (Leuci et al., 2013; Schuch et al., 2019). A low number of cases of primary syphilis has been reported in the literature, with percentages ranging from 2.8% to 17% of the entire series samples (Leuci et al., 2013;

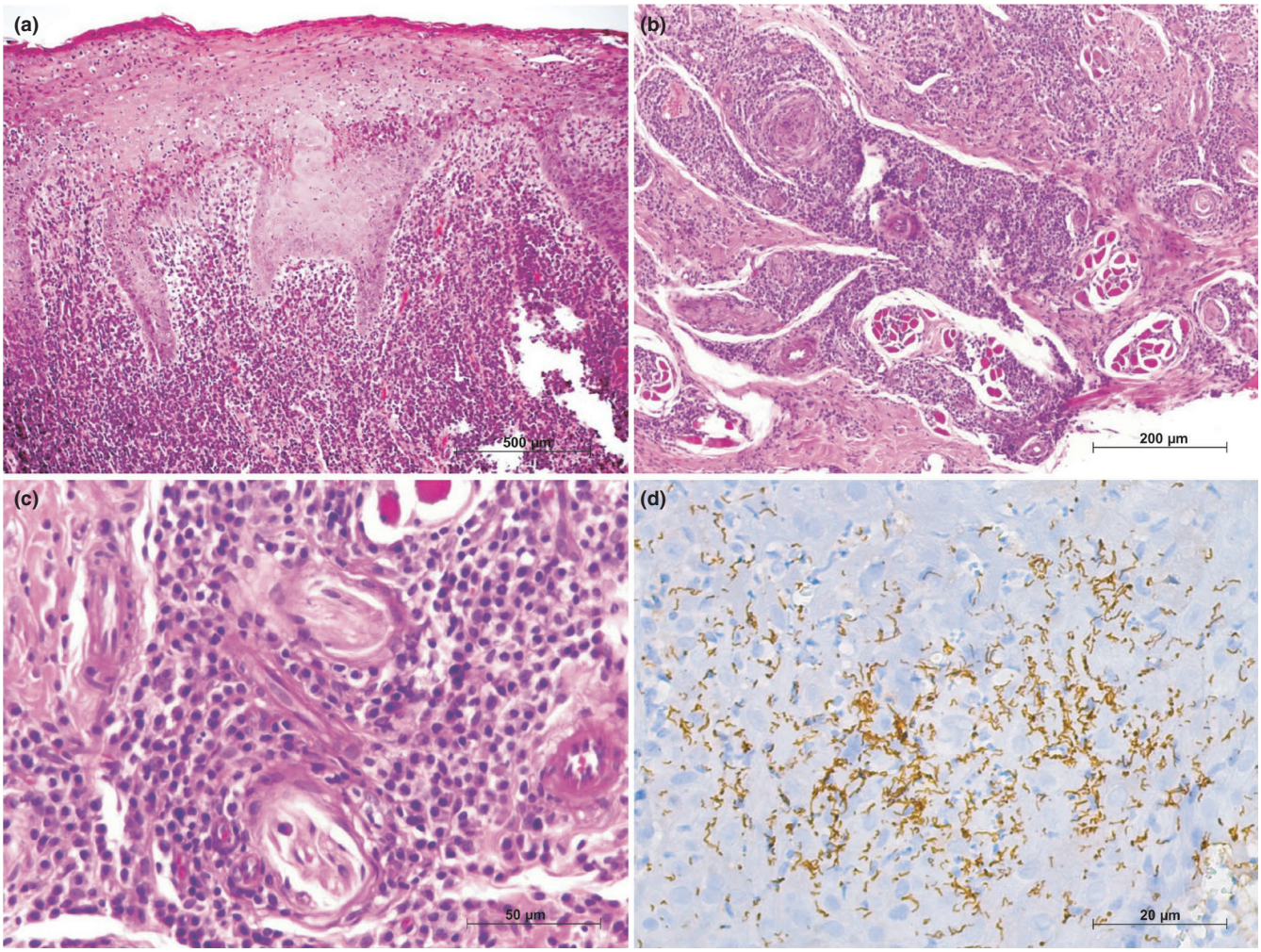

FIGURE 6 Histopathological and immunohistochemical aspects of the secondary stage of acquired oral syphilis. (a, b) Low power view of the lesion showing stratified squamous epithelium of irregular thickness with a pseudoepitheliomatous pattern and a plasmacytic inflammatory infiltrate on the connective tissue with the presence of a microabscess. (c) High-power photomicrograph showing details of a predominantly plasma cellular infiltrate (hematoxylin and eosin stain; a, ×4; b, ×10; and c, ×40). (d) Numerous spirochetes showing positivity for the *T. pallidum* antibody (DAB; ×100)

Thums et al., 2021). A review that compiled single cases of AOS also demonstrated that 55% were secondary syphilis, whereas 12.9% of the cases were individuals in the primary stage of the disease (Schuch et al., 2019). This is certainly due to the fact that primary syphilis becomes clinically evident 3–90 days after the initial exposure, and the infection can be completely asymptomatic (Little, 2005; Schuch et al., 2019). Lastly, three cases of unknown duration or late syphilis, also known as tertiary syphilis, were demonstrated in this series. They are generally documented in low-income countries. Considering that the incubation period lasts more than 1 year and can be as long as 25–30 years, complications and morbidity are expected at this stage (Little, 2005).

The differential diagnosis of AOS might consider a plethora of erythematous and erosive lesions, nodular/papular lesions, gray or white lesions, and ulcerative lesions (de Arruda et al., 2021; Schuch et al., 2019). In this study, oral health providers listed a variety of diagnostic possibilities, including infectious diseases, oral potentially malignant disorders, and malignancies. Although the diagnosis of AOS is not straightforward, several approaches to the detection of *T. pallidum* are available (Centers for Disease Control & Prevention, 2015; de Arruda et al., 2021). However, serological tests continue to be the gold standard (Lampros et al., 2021; Schuch et al., 2019; Thums et al., 2021). Meanwhile, silver staining or immunohistochemistry may be used for tissue sections, since histopathological findings are nonspecific and mimic other conditions (Smith et al., 2021).

Concerning the treatment of AOS, the medication regimens used in South American countries and in patients of this series are aligned with the guidelines of CDC endorsing that the mainstay of therapy is parenteral penicillin G (Centers for Disease Control & Prevention, 2015; Ghanem et al., 2020). A concentration of penicillin above 0.018 mg/L is considered treponemicidal, but this drug is very efficient in early syphilis and less effective in advanced stages (Ficarra & Carlos, 2009). However, with the global shortage and rising costs of penicillin, alternative treatment options, including cefixime, for the management of early syphilis have emerged (Stafylis et al., 2021).

Considering that AOS remains a public health conundrum, especially in low- and middle-income economies (Kenyon et al., 2016; Newman et al., 2015; Zoni et al., 2013), continuous investments in these countries are encouraged (Ghanem et al., 2020; Schmidt et al., 2019). Hence, evidence suggests that testing is a key strategy for the prevention and treatment of HIV and syphilis in low- and middle-income countries (Adawiyah et al., 2021). Likewise, syphilis vaccine development will complement syphilis prevention initiatives with a public health focus in order to offer a two-pronged approach to curbing the spread of the disease worldwide (Cameron, 2018).

Limitations of the present study included the fact that the follow-up of affected individuals was unfeasible since the investigation involved only diagnostic data from oral diagnosis services. After the diagnosis, patients are usually referred to hospitals in their respective countries for investigation of other STI and adequate treatment of AOS. Some data were missing, a fact inherent to the retrospective nature of the present study. Also, the frequency of the disease at a population level seems to be dependent on various additional factors, including socioeconomic and cultural factors, so that the prevalence and incidence cannot be accurately estimated. Therefore, we strongly emphasize that the notification of AOS in South America is important for the implementation of preventive measures and an early diagnosis that may lead to more effective treatments and better outcomes for this population.

In summary, this multicenter study highlights the spread of AOS infection among individuals of both sexes in South America. Availability of diagnostic tools for adequate disease screening, surveillance, and counseling of affected individuals should be directives included in health policies of low- and middle-income countries.

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CONFLICT OF INTEREST

None to declare.

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SUPPORTING INFORMATION

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