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Diagnostic approaches in unsuspected oral lesions of syphilis

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Abstract. Awareness of the increased prevalence of syphilis is essential for early diagnosis and treatment, and to prevent the spread of the disease. Although serological studies are the primary tool used to confirm the diagnosis of secondary syphilis, biopsy of unsuspected oral lesions is not uncommon in the routine oral pathology laboratory. In these cases, histopathological characteristics are likely to indicate the possibility of syphilis, and an immunohistochemical reaction can confirm it. The aim of the present study was to highlight the histological features and test the efficacy of immunohistochemistry in the detection of *Treponema pallidum* in oral lesions biopsied with the assumption of a non-syphilitic disease. Thirty-nine tissue samples from patients for whom the possibility of syphilis was suggested on the basis of histopathological findings, were retrieved from the surgical oral pathology service files and submitted to immunohistochemical staining for *T. pallidum*. The study was approved by the institutional ethics committee. Eighteen of the tissue samples were positive for *T. pallidum*. Following this, the contributing clinicians were contacted to check whether they had asked for serological examinations when the diagnostic report was received; for all 18 positive cases, the clinicians confirmed that the patients had tested positive at that time. This study shows the importance of clinical–pathological correlation and the value of immunohistochemistry in the diagnosis of unsuspected syphilis.

Keywords: Treponema; *Treponema pallidum*; mucous patch; oral infections; sexually transmitted diseases..

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Syphilis is a systemic infectious disease caused by the filamentous, anaerobic spirochaete *Treponema pallidum*. The disease can be transmitted sexually (acquired syphilis) or vertically via the placenta (congenital syphilis).[1] Although effective therapy has been available for a long time, the incidence of syphilis has increased worldwide in the past decade.[2–4]

Three main stages with different clinical presentations and infectivity are considered in the development of syphilis. Oral lesions may occur at any of the three main stages of the clinical course, including the primary, secondary, and tertiary phases,[5] with increased frequency in the secondary phase, occurring in 30–50% of cases. Owing to the variability in their appearance, oral lesions may represent a diagnostic challenge.[3,4] However, when a biopsy is performed, certain histological features can be quite indicative of oral syphilis, such as a chronic inflammatory infiltrate composed mainly of plasma cells in a perivascular location with a lichenoid or band-like appearance, epithelial hyperplasia, exocytosis or micro-abscesses in

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the epithelium, and endarteritis or neuritis. According to the phase of the disease, other features, such as giant cells and ulceration, may be present.[6–9]

When syphilis is suspected, serological testing should be performed immediately. The VDRL (Venereal Disease Research Laboratory), RPR (rapid plasma reagin), and FTA-ABS (fluorescent treponemal antibody absorption) tests are the most widely used; the former two are non-specific tests and the latter is a specific test. In addition, primary or secondary lesions can be diagnosed through dark-field examination, which shows the typical motile spirochaetes; however this is seldom performed today because of technical difficulties.[2,10]

An immunohistochemical reaction using an anti-treponemal antibody is highly specific, with specificity ranging from 74% to 94%.[7,11,12] A few studies have shown that both the histological pattern of syphilis and immunohistochemical detection by the antibody in biopsy specimens is effective in the diagnosis of syphilis, but most studies were performed in non-mucosal tissue.[9,11]

In the present study, a series of oral biopsies in which the initial clinical impression was not syphilis but for which syphilis was then considered as a result of findings on histopathological analysis, were submitted to immunohistochemistry for the detection of *T. pallidum*.

Materials and methods

All cases diagnosed with a chronic inflammatory process and for whom the possibility of syphilis was noted on the diagnosis report, were retrieved from the archives of the university oral pathology department; these records were from a period of 5 years (2005–2010). The study was approved by the university ethics committee. A total of 39 cases were retrieved. Haematoxylin and eosin (H&E) stained slides were reviewed to confirm the histological hypothesis of syphilis, and tissue specimens from the cases were then submitted to immunohistochemical staining for anti-*T. pallidum* antibody. The clinical data of the patients were obtained from the medical records. Because this oral pathology service receives biopsies from different clinics and hospitals, the medical care provider was contacted to confirm that the patient had been tested serologically for syphilis immediately following receipt of the report. The cases retrieved had not been submitted to immunohistochemistry at the time of this first diagnosis because antibody was not available at that time.

Immunohistochemistry

For immunohistochemistry, 3-μm thick sections were subjected to streptavidin–biotin staining. Briefly, sections were incubated for 60 min at room temperature with the polyclonal antibody anti-*T. pallidum* (Biocare Medical, Walnut Creek, CA, USA) at a dilution of 1:100, followed by incubation with the streptavidin–biotin complex (Kit LSAB Peroxidase K0690; Dako North America, Inc., Carpinteria, CA, USA). Next, sections were incubated for 10 min with diaminobenzidine (Liquid DAB; Dako North America, Inc.) and counterstained with Mayer's haematoxylin. Negative controls were treated as above, but were incubated in a solution of 1% bovine serum albumin (BSA) in Tris–HCl pH 7.4, instead of the primary antibody. Tissues known to be positive for *T. pallidum* were used as positive controls.

Results

A total of 18 out of the 39 cases retrieved were positive for the anti-*T. pallidum* antibody. According to information obtained subsequently from the contributors, these 18 cases had tested positive for syphilis at the time of the diagnosis and had been diagnosed with secondary syphilis. None of the remaining 21 cases tested positive. Thus, the 18 positive cases represented patients with unsuspected lesions of secondary syphilis who had received diverse differential diagnoses before the biopsy. These included histoplasmosis, viral infection, neurilemmoma, lymphoma, pemphigus vulgaris, cicatricial pemphigoid, squamous cell carcinoma, lichen planus, gonorrhoea, hyperkeratosis, Behçet's syndrome, and tuberculosis. In only two cases was a possibility of syphilis raised, but as a secondary clinical impression (Table 1). Differential diagnoses of the negative cases were pemphigus, pemphigoid, lichen planus, squamous cell carcinoma, psoriasis, keratoacanthoma, histoplasmosis, and ulcer. Two patients were black and 16 were white, and the majority of the patients were male (83.3%); the mean age was 43.16 years (range 17–56 years). The lip was the predominant site of the lesions (50%), followed by the tongue (33.3%). Clinically the lesions presented as ulcers, erosions, and, rarely, as nodules. A few of these lesions had been photographed (see Fig. 1).

Table 1. Clinical data of the cases positive for *Treponema pallidum*.

Patient	Gender	Age (years)	Site	Clinical diagnosis	Serologic testing for syphilis
1	M	51	Upper and lower lip	Histoplasmosis	VDRL
2	M	45	Lower lip	Viral infection	VDRL
3	M	45	Tongue dorsum	Viral infection	VDRL
4	M	46	Tongue dorsum	Neurilemmoma	RPR
5	M	45	Buccal mucosa	Lymphoma	VDRL
6	M	45	Gingiva	Lymphoma	VDRL
7	M	42	Lower lip	Chronic ulcer	VDRL
8	F	28	Lower lip	Pemphigus/pemphigoid	RPR
9	F	31	Tongue dorsum	Pemphigus/pemphigoid	RPR
10	M	41	Upper lip	Erosive lichen planus	RPR
11	M	54	Lower lip	Tuberculosis/Syphilis	VDRL
12	M	46	Tongue, lateral border	Squamous cell carcinoma	VDRL
13	M	37	Tongue, lateral border	Squamous cell carcinoma/ulcer	VDRL
14	M	17	Lower lip	Hyperkeratosis	VDRL
15	M	41	Lower lip	Ulcer/pemphigoid	VDRL
16	F	52	Buccal mucosa	Ulcer/Behçet's syndrome	VDRL
17	M	55	Tongue dorsum	Gonorrhoea/syphilis	VDRL
18	M	56	Lower lip	Hyperkeratosis	VDRL

M, male; F, female; VDRL, Venereal Disease Research Laboratory; RPR, rapid plasma reagin.