J Oral Pathol Med (2004) 33: 286–91

www.blackwellmunksgaard.com/jopm

The histopathology of syphilis of the oral mucosa

A. W. Barrett[1], M. Villarroel Dorrego[1], T. A. Hodgson[2], S. R. Porter[2], C. Hopper[3], A. S. Argiriadou[2], P. M. Speight[1]

[1]*Oral and Maxillofacial Pathology,* [2]*Oral Medicine, and* [3]*Maxillofacial Surgery Units, Eastman Dental Institute for Oral Healthcare Sciences, UCL, University of London, 256 Grays Inn Road, London WC1X8LD, UK*

BACKGROUND: Reported cases of syphilis in the United States, Europe and elsewhere are increasing in number. Clinical manifestations are protean, and oral biopsies may be taken where the diagnosis is unsuspected, but data on the histopathology of oral mucosal syphilis are sparse.
METHODS: The histopathology of five oral lesions in patients with serologically proven syphilis was reviewed.
RESULTS: There were two cases of primary syphilis, one secondary and two tertiary. Epithelial hyperplasia was present in three cases, and was pseudocarcinomatous in one case of primary syphilis, and psoriasiform in the secondary lesion, where heaped-up epithelium surrounded a defined crater covered by flatter epithelium. Plasma cell (primary and secondary disease) and granulomatous (tertiary) infiltrates were prominent. Other features observed were endarteritis (5/5), plasma cell neuritis (3/5) and spirochetes (4/5).
CONCLUSIONS: Although no single microscopic feature is specific, a diagnosis of syphilis should be considered where there is unusual epithelial hyperplasia, granulomatous or plasma cell-predominant chronic inflammation, endarteritis and neuritis.
J Oral Pathol Med (2004) **33**: 286–91

Keywords: mouth mucosa; pathology; surgical; syphilis

Introduction

Syphilis is an infectious disease, which can be congenital or acquired, caused by the spirochete *Treponema pallidum*. Acquired syphilis is much commoner and is the result of sexual contact with, or blood transfusion from, an infected person. The disease may present in the primary, secondary or tertiary stage. Following the Great War (1914–1918), the incidence of the disease rose in industrialized countries, but declined after the Second World War (1939–1945) because of the widespread introduction of antibiotics. Subsequently there has been a gradual increase in new cases of syphilis world wide, and although overall registrations fluctuate (1), syphilis is still the fourth most commonly diagnosed infectious disease in the United States (2). There has been an alarming increase in reported cases in Russia (1). In England between 1996 and 2001, there was a 374% increase in the number of cases of infectious syphilis (3), with the number of diagnoses of primary and secondary syphilis rising by 144% (252–614) in males and 36% (75–102) in females between 2000 and 2001 alone. The rise was particularly high (187%) in homosexual men. In 2001, 86% of cases were diagnosed in males and reflected outbreaks in the London and north-west regions (4, 5).

The oral cavity is the commonest extragenital site of infection (2), and although oral manifestations are rare, the importance of considering the diagnosis has recently been highlighted (6). Primary syphilis, which may present extragenitally in 10% of cases (7), appears orally most commonly as a crateriform and indurated chancre, typically located on the lips, tongue or palate (2, 6–8). Secondary syphilis produces multiple lesions often affecting several oral sites, but most characteristically manifests as white plaques (mucous patches), which fuse to form 'snailtrack' ulcers usually situated on the lips, palate or tongue (2, 7–9). However, macroglossia (9), painful fissuring (9) and papular lesions of the anterior two-thirds of the dorsum of the tongue (10) have also been reported. There may be a symmetric arrangement of secondary oral lesions (7). Tertiary oral mucosal lesions are usually palatal (the commonest site for gummas) or lingual (luetic glossitis and potentially malignant leukoplakia) and comprised 62/81 (77%) of cases in the series reported by Meyer & Shklar (8) in the 1960s. Oral lesions of tertiary syphilis are now uncommon, but are still occasionally reported (11).

The diagnosis is often made on clinical and serological grounds without recourse to biopsy. However, because of the protean clinical manifestations and rarity of oral lesions, biopsies may be taken where the diagnosis is unsuspected. The aim of this study is therefore to describe the histopathological features of oral mucosal syphilis.

Correspondence: Dr A.W. Barrett, Oral and Maxillofacial Pathology Unit, Eastman Dental Institute for Oral Healthcare Sciences, University College London, 256 Grays Inn Road, London WC1X8LD, UK. Tel.: +44 20 79151055 or +44 20 76796011. Fax: +44 20 79151213. E-mail: A.Barrett@eastman.ucl.ac.uk
Accepted for publication November 6, 2003

Materials and methods

Approval was sought and granted from the Joint Research and Ethics Committee of the Eastman Dental Institute and Hospital, and the Research and Development Directorate of the University College London Hospitals Trust. Cases diagnosed as syphilis accessioned between 1947 and 2001 were retrieved from departmental archives. Clinical details were gleaned from the request forms or the case notes. Original histological sections were reviewed, and where necessary further 5 μm sections were prepared and stained with hematoxylin and eosin, or by periodic acid-Schiff (PAS), Ziehl–Neelsen (ZN) and Warthin–Starry (WS) methods. Immunohistochemistry carried out at the time of diagnosis was performed using a standard streptavidin-biotinylated immunoperoxidase technique. For this study, new sections from each case were also stained with a rabbit polyclonal antiserum to *T. pallidum* (ImmunologicalsDirect.com). This was used at a concentration of 1/1000 following antigen retrieval by microwaving sections in high pH buffer for 25 min. Antigen-binding sites were visualised with the EnVision+ peroxidase system (Dako Ltd, Ely, UK) (12). Sections were analysed with a Zeiss Axioskop microscope and photographed using either an Olympus DP11 digital or Zeiss MC80 DX conventional camera.

Results

Five cases with satisfactory clinical and serological evidence of syphilis were retrieved. Two patients were female and all were white. The clinical and serological features and diagnoses are summarised in Tables 1 and 2, respectively.

Case 1

A 59-year-old housewife presented in 1957 with a painless soft tissue swelling and erythema of the right soft palate of 6 weeks duration. There was no ulceration and the clinical diagnosis was of a pleomorphic adenoma. Microscopy showed oral mucosa covered by intact, mildly hyperplastic epithelium with, predominantly in the submucosa, a dense, diffuse chronic inflammatory cell infiltrate (Fig. 1). This was composed of histiocytes with interspersed lymphocytes, plasma cells, eosinophils and neutrophils, and foci of necrosis were noted. The infiltrate disrupted the minor salivary glands; there were many Langhans-type giant cells with peripherally placed nuclei and scattered granulomas of various size, some associated with globules of fat. Several blood vessels were obliterated by endarteritis. PAS, ZN and immnohistochemistry for *T. pallidum* were negative, but WS stains detected occasional spirochetes within histiocytes and endothelial cells. The main differential diagnosis was tuberculosis, but this was excluded by absence of caseation and her seropositivity for syphilis (although for which tests are not recorded). In addition, she subsequently developed nodular gummatous lesions of the skin. The oral diagnosis was thus that of an early gumma of a tertiary sphilis. Treatment with procaine penicillin (600 000 IU for 16 days) caused clinical resolution of the oral and skin lesions. It was unknown how she had acquired the disease.

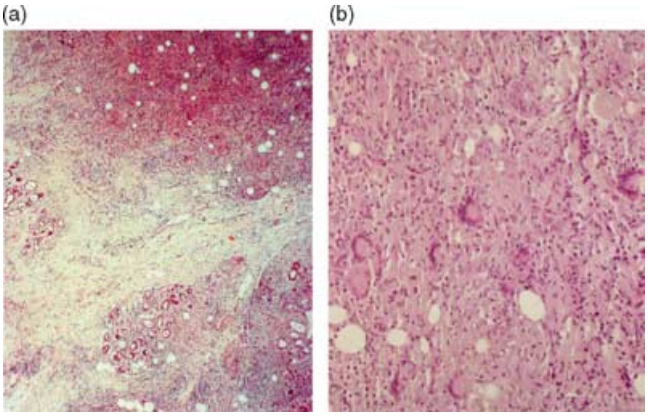

Figure 1 Tertiary syphilis. (a) Palatal lesion showing dense infiltrates of chronic inflammatory cells disrupting minor salivary glands and submucosal fat. (b) The infiltrate is composed principally of histiocytes amongst which are multinucleate giant cells, many of Langhans type. Case 1: hematoxylin and eosin, field width (a) 3.5 mm (b) and 0.4 mm.

Table 1 Clinical details of five cases of oral mucosal syphilis

Case	*Age*	*Sex*	*Presentation*	*Duration*
1	59	F	Painless swelling of soft palate	6 weeks
2	60	F	Erythema and ulceration of soft palate	'Several months'
3	62	M	Ulceration of upper labial mucosa	7 weeks
4	31	M	Erythema of anterior palatal gingiva	5 weeks
5	55	M	Symmetrical ulcers of ventral tongue	Unknown

Table 2 Serological details and diagnoses of five cases of oral mucosal syphilis

Case	*VDRL*	*RPR*	*TPHA*	*FTA-abs*	*Diagnosis*
1	Seropositive, but unknown for which tests				Tertiary
2	Negative	Not done	+	+	Tertiary
3	Not done	+ (1/256)	+	+	Primary
4	Not done	+ (1/16)	Negative	+	Primary
5	Not done	+ (1/32)	+	+	Secondary

Case 2

In 1975, a 60-year-old female who had had congenital syphilis treated with penicillin in 1949 presented with erythema and ulceration of the soft palate of 'several months' duration. She had previously had a granulomatous lesion of the cheek reported as 'tuberculoid, possibly sarcoid or lupus vulgaris'. Sputum culture and a Mantoux test were negative, as was venereal diseases research laboratory (VDRL) serology (Table 2), but the more specific *T. pallidum* haemagglutination assay (TPHA) and fluorescent treponemal antibody absorbed (FTA-abs) tests were positive. A diagnosis of tertiary syphilis was made. It was uncertain whether her previous penicillin treatment had been inadequate, or whether she had been reinfected after antibiotic treatment and had progressed to tertiary syphilis in the ensuing years before representing. Histologically, there was little epithelium, and that present was inflamed but otherwise unremarkable. The lamina propria was

extensively infiltrated by sheets of histiocytes forming granulomas, with scattered multinucleate giant cells, some of Langhans type. Lymphocytes with a perivascular distribution, interspersed plasma cells, neutrophils and endarteritis were also noted, but there was no necrosis. There was lymphatic dilation and the inflammatory infiltrate extended into the submucosa to involve minor salivary glands. PAS, ZN and WS stains, and immnohistochemistry for *T. pallidum*, were negative. The lesions resolved with unspecified penicillin therapy.

Case 3

In 1999 a 61-year-old homosexual, HIV-negative male patient presented with a painful ulcer of the upper lip of approximately 7 weeks duration. Although he had recently lost weight, there were no other systemic signs or symptoms. The clinical diagnosis was of traumatic ulceration, squamous cell carcinoma or HIV-related disease. Serology was positive (Table 2) and a diagnosis of primary syphilis was made, after which he admitted having had unprotected oral sex in India 9 weeks prior to presentation, and a previous episode of syphilis. Microscopy revealed oral mucosa covered by hyperplastic, in places pseudocarcinomatous, parakeratinised stratified squamous epithelium (Fig. 2), which was extensively ulcerated and replaced by a fibrinopurulent slough. There were superficial microabscesses, and PAS-positive fungal hyphae were identified. The rete morphology was sometimes bulbous, and reactive keratinocyte atypia was frequently observed. The lamina propria and striated muscle were densely infiltrated by chronic inflammatory cells, principally plasma cells, but immunohistochemistry for immunoglobulin, kappa and lambda light chains showed no light-chain restriction. Perivascular and more diffuse lymphoplasmacytic infiltrates extended into the striated muscle. Occasional small granulomas, composed of histiocytes and giant cells of Langhans type, endarteritis (Fig. 3) and plasma cell neuritis were observed. A ZN stain was negative, but WS and immnohistochemistry for *T. pallidum* revealed scattered spirochetes, mainly within keratinocytes but also within histiocytes in the superficial lamina propria. The clinical features, treatment and course of this case have been previously described in detail elsewhere (6).

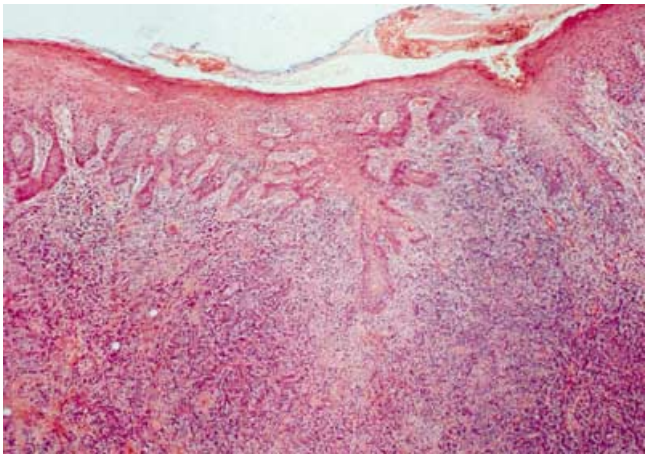

Figure 2 Primary syphilis. Labial mucosa covered by parakeratinised stratified squamous epithelium showing pseudocarcinomatous hyperplasia. There is a dense chronic inflammatory cell infiltrate in the lamina propria, which extends into the submucosa. Case 3: hematoxylin and eosin, field width 2.2 mm.

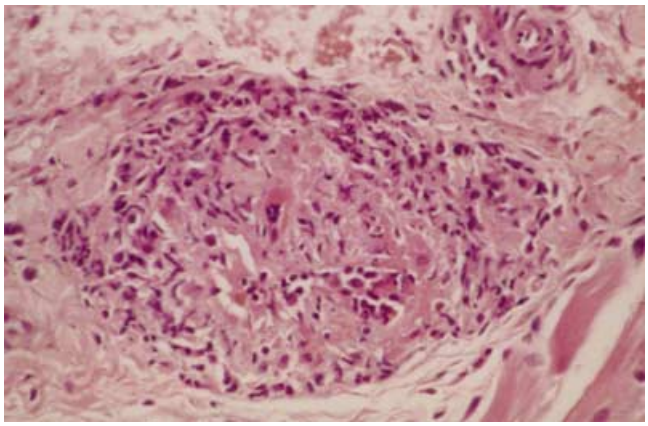

Figure 3 Primary syphilis. Endarteritis in a blood vessel within the labial striated muscle (bottom right of field). Case 3: hematoxylin and eosin, field width 0.4 mm.

Case 4

In 1999 a 31-year-old homosexual, HIV-negative male presented with a demarcated zone of inflamed, swollen gingivae on the palatal aspect of the maxillary central incisors of 5 weeks duration. There were no other systemic signs or symptoms. He had recently returned from Mexico, where he had had unprotected oral sex with several males. The clinical diagnosis was of primary or secondary syphilis, other vasculitic lesion, Kaposi's sarcoma, vesiculobullous lesion or infection. Two punch biopsies of the lesion were taken under local anesthesia. Histopathology revealed oral mucosa covered by hyperplastic, parakeratinised stratified squamous epithelium, which was ulcerated and replaced by a fibrinopurulent slough. Within the lamina propria there were focal, perivascular infiltrates composed of lymphocytes and plasma cells, with scattered eosinophils. Endarteritis and plasma cell neuritis were again noted, but there were no granulomas. A PAS stain was negative. Serology was positive (Table 2), and although immnohistochemistry for *T. pallidum* was equivocal, a WS stain revealed occasional spirochetes within histiocytes of the lamina propria. A diagnosis of primary syphilis was made. The clinical features, treatment and course of this case have been previously described in detail elsewhere (6).

Case 5

A married 56-year-old male bus driver presented in 2000 with bilateral, furrowed, indurated areas on the ventral surface of the tongue. The duration of these lesions was unknown, but a few weeks previously, he reported a nasolabial rash and desquamation of the soles of the feet. A lingual biopsy was taken principally to exclude squamous cell carcinoma. Histopathology of the lesion from the right showed oral mucosa covered by parakeratinised stratified squamous epithelium, which showed a heaped-up,

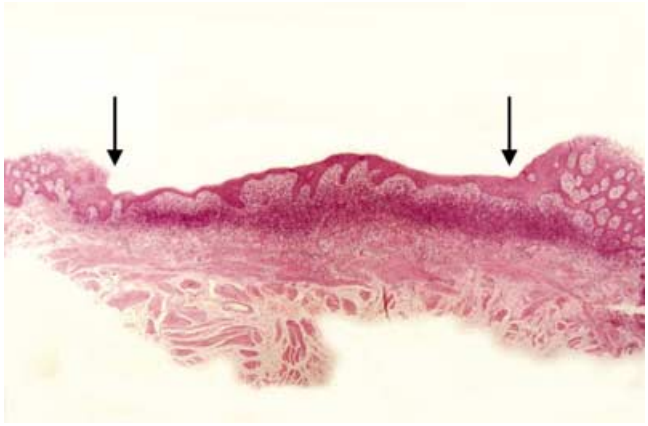

Figure 4 Secondary syphilis. Lingual mucosa covered by parakeratinised stratified squamous epithelium. There is a central demarcated zone (arrows) covered by thinner epithelium, which nevertheless shows rete hyperplasia. Peripherally, the epithelium is heaped-up and more prominently hyperplastic. There is a dense, band-like infiltrate of chronic inflammatory cells in the lamina propria, which extends into the lingual musculature. Case 5: hematoxylin and eosin, field width 9.0 mm.

psoriasiform hyperplasia at the edges but, centrally, a depressed, demarcated zone resembling a crater covered by thinner, flatter and less markedly hyperplastic epithelium (Fig. 4). There was, however, no ulceration, and although there were superficial microabscesses, no fungal hyphae were identified. The lamina propria was densely infiltrated by chronic inflammatory cells, principally plasma cells, forming a dense band (Fig. 4), but immunohistochemistry showed no light-chain restriction. A perivascular distribution of lymphoplasmacytic infiltrates was noted; the plasma cells extended deep into the lingual musculature with neuritis (Fig. 5) and endarteritis again present. There were no discrete granulomas, but immunohistochemistry did show clusters of CD68-positive histiocytes in the connective tissue papillae. A WS stain revealed scattered bacteria (Fig. 6), but immnohistochemistry for *T. pallidum* identified abundant spirochetes, mainly within the stratified squamous epithelium and particularly within and between the keratinocytes

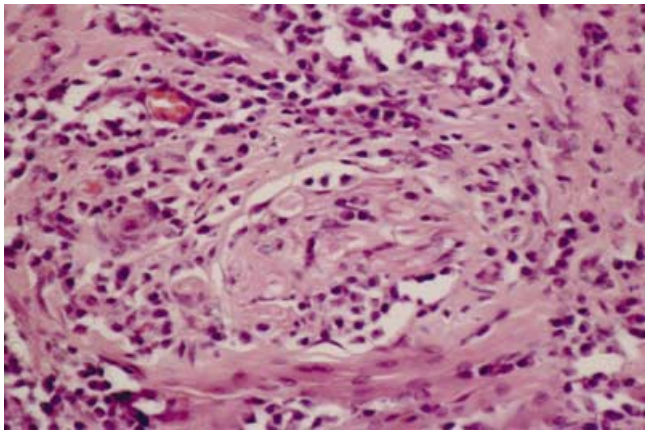

Figure 5 Secondary syphilis. Plasma cells have infiltrated striated muscle (bottom of field) and a small nerve. Case 5: hematoxylin and eosin, field width 0.4 mm.

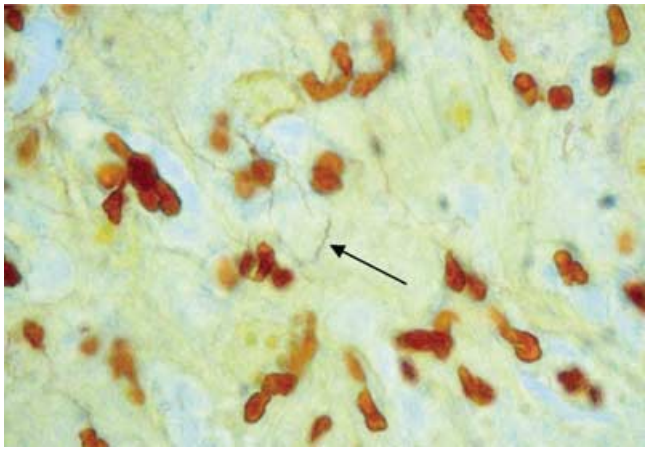

Figure 6 Coiled spirochetes (arrow) in the superficial lamina propria. case 5: WS, field width 0.1 mm.

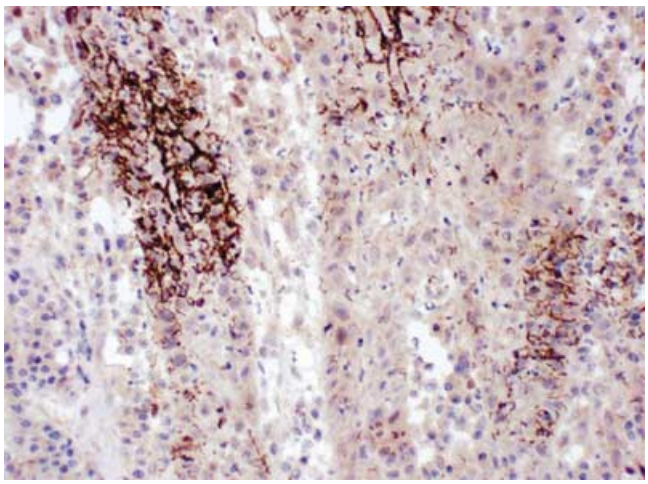

Figure 7 Spirochetes in the stratified squamous epithelium of case 5, detected with an antibody to *T. pallidum*. Micro-organisms are most abundant in the more superficial part of the rete ridges, where they form clumps. EnVision+ immunoperoxidase, field width 1.0 mm.

of the more superficial strata, where they often formed clumps (Fig. 7). However, scattered microbes were also present in plasma cells (Fig. 8). Serology was positive (Table 2) and a diagnosis of secondary syphilis was made. Subsequent questioning revealed frequent encounters with female prostitutes. Treatment was with intramuscular procaine penicillin (900 mg daily for 10 days), oral probenecid (500 mg b.i.d. 3/52) and intramuscular benzyl penicillin (800 mg daily for 10 days).

The common histopathological features of the five cases are summarised in Table 3.

Discussion

Detailed descriptions of the histopathological features of oral syphilis are scarce, possibly because of the rarity with which oral disease is biopsied. One of the key microscopic features (Table 3) is plasma cell infiltration (13), at least in primary and secondary disease. The presence of plasma cells

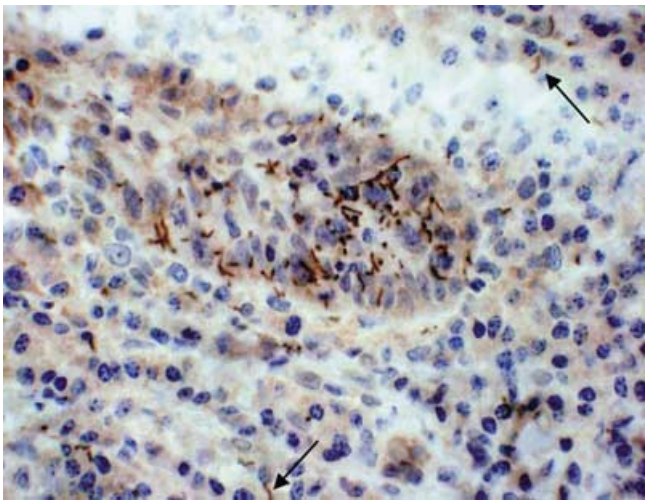

Figure 8 At higher power, spirochetes are also present in plasma cells in the lamina propria. EnVision+ immunoperoxidase, field width 0.5 mm.

in skin is unusual and immediately raises the possibility of syphilis, particularly if there is a perivascular distribution (14, 15). Plasma cells are, however, common in oral biopsies, especially those taken from the gingiva, and their significance may be overlooked. It is a plasma cell infiltrate, which extends deeply into the submucosa that should perhaps bring the diagnosis to mind. Syphilis should also be considered in apparently non-specific oral ulcers in HIV-positive patients (16, 17) and those in high risk groups (such as cases 3 and 4). Coincident candidal infection suggests that case 3 was immunocompromised, but several HIV tests were negative (6).

Our findings are in general agreement with those of Meyer & Shklar (8) who reported the features of primary and secondary disease to be essentially non-specific, but the tertiary lesion to be the most obviously granulomatous and populated with Langhans-type giant cells (Fig. 1), although this is not always the case (18). Features of chronic granulomatous inflammation without significant necrosis are typical of early nodular lesions of tertiary syphilis and the sparse numbers of plasma cells can mask the diagnosis (15), thus the features mimick tuberculosis, sarcoidosis or a deep mycosis (8). Furthermore, as in the two cases reported here, tertiary lesions are only sparsely populated with spirochetes (2). Easy, consistent and reliable identification of *T. pallidum*, however, remains problematic.

The WS method is a silver impregnation technique, which has identified *T. pallidum* in surface epithelium (10, 15–17), intercellular spaces adjacent to blood vessels, macrophages, endothelial cells and plasma cells (14) (Fig. 6). Detection is not straightforward because the microorganisms may be absent or scarce, or because of technical difficulties with the laboratory procedure. Also, the stain is not specific, and consequently other species of spirochetes, which inhabit the oral cavity, may be labelled (2). Although specific antibodies combined with immunohistochemistry offer the potential to improve matters (19), few are currently commercially available. The antibody used in this study was derived using an immunogen of highly purified *T. pallidum*, and the purified IgG fraction of the antiserum is 95% pure. The striking infestation of bacteria present in the hyperplastic stratified squamous epithelium covering the oral mucosa in case 5 (Figs. 7 and 8), the patient with secondary syphilis, is a feature not previously reported. However, the antiserum may still cross-react with related microorganisms (20) and this, combined with the fact that the pattern of WS staining in the same biopsy was different, suggests that not all the spirochetes in Figs. 7 and 8 are *T. pallidum*.

There is no previous description of the curious pattern of epithelial depression seen in case 5 (Fig. 4) or neuritis (Fig. 5) in primary and secondary syphilis. Neurological signs and symptoms are, of course, a well-known (although now almost historic) feature of tertiary syphilis. Evidently, histological evidence of nerve damage can be seen in earlier stages of disease. The tongue is often involved in secondary syphilis (8), and ischemia consequent to endarteritis possibly accounts for the demarcated epithelial-lined crater in case 5 (Fig. 4). The morphology suggests this change precedes ulceration. For the purposes of comparison, it is unfortunate that the lingual lesions of secondary syphilis reported by Fiumara et al. (10) and Mani (9) were not biopsied.

The symmetric arrangement of multiple lesions produced a clinical history suggestive of secondary syphilis in case 5 (7, 15), and psoriasiform hyperplasia and superficial and deep plasma cell infiltrates in a band-like pattern are features of secondary lesions in the skin (15). However, we also noted deep plasmacytic infiltrates as a feature of primary as well as secondary oral syphilis. Other microscopic parallels with skin lesions of syphilis are the potential for confusion with lymphoma, and the presence of pseudocarcinomatous hyperplasia. Lymphoma may enter the differential diagnosis of cutaneous secondary syphilis (14, 15), and we considered lymphoma in cases 3 (primary) and 5 (secondary). Absence of light-chain restriction and the results of serology helped exclude this possibility. Pseudocarcinomatous hyperplasia, seen in case 3 (Fig. 2), may be a feature of epidermis adjacent to chancres of the skin (15).

Table 3 Histopathological features common to at least 3/5 cases of oral mucosal syphilis

Microscopic feature	*Case 1 (3°)*	*Case 2 (3°)*	*Case 3 (1°)*	*Case 4 (1°)*	*Case 5 (2°)*
Unusual epithelial hyperplasia	–	–	++	+	++
Infiltrates of histiocytes or plasma cells in a diffuse and/or perivascular pattern, extending into and disrupting submucosal structures	Histiocytes	Histiocytes	Plasma cells	Plasma cells	Plasma cells
Langhans-type giant cells	++	++	+	–	–
Endarteritis	+	+	+	+	+
Neuritis	–	–	+	+	+
Demonstrable spirochetes	+	–	+	+	++

In conclusion, these five cases suggest that there is no single microscopic feature specific to syphilis. However, in combination (Table 3), and if considered with clinical information, the microscopic features can provide reasonable grounds for proceeding to serology for syphilis if this has not already been requested.

References

1. World Health Organization. Syphilis. In: *Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections: Overview and Estimates.* Geneva: World Health Organization, 2001.
2. Siegel MA. Syphilis and gonorrhea. *Dent Clin North Am* 1996; **40**: 369–83.
3. Adler MW. Sexual health – health of the nation. *Sex Transm Infect* 2003; **79**: 85–7.
4. Dodds JP, Nardonne A, Mercey D, Johnson AM. Increase in high risk sexual behaviour among homosexual men, London 1996–8: cross sectional questionnaire study. *Br Med J* 2000; **320**: 1510–1.
5. Doherty L, Fenton KA, Jones J, et al. Syphilis: old problem, new strategy. *Br Med J* 2002; **325**: 153–6.
6. Alam F, Argiriadou AS, Hodgson TA, Kumar N, Porter SR. Primary syphilis remains a cause of oral ulceration. *Br Dent J* 2000; **189**: 352–4.
7. Laskaris G. Oral manifestations of infectious diseases. *Dent Clin North Am* 1996; **40**: 395–423.
8. Meyer I, Shklar G. The oral manifestations of acquired syphilis. *Oral Surg Oral Med Oral Pathol* 1967; **23**: 45–57.
9. Mani NJ. Secondary syphilis initially diagnosed from oral lesions. *Oral Surg Oral Med Oral Pathol* 1984; **58**: 47–50.
10. Fiumara NJ, Grande DJ, Giunta JL. Papular secondary syphilis of the tongue. *Oral Surg Oral Med Oral Pathol* 1978; **45**: 540–2.
11. Aarestrup FM, Vieira BJ. Oral manifestation of tertiary syphilis. *Braz Dent J* 1999; **10**: 117–21.
12. Vyberg M, Nielsen S. Dextran polymer conjugate two-step visualization system for immunohistochemistry. A comparison of EnVision+ with two three-step avidin-biotin techniques. *Appl Immuno* 1998; **6**: 3–10.
13. Regezi JA, Sciubba JJ. Ulcerative conditions. In: *Oral Pathology. Clinical Pathologic Correlations.* Philadelphia: W.B. Saunders, 2000; 37.
14. Weedon D. Spirochetal infections In: *Skin Pathology.* Edinburgh: Churchill Livingstone, 1997; 549–54.
15. McKee P. Infections diseases In: *Pathology of the Skin*. London: Gower 1996; 4.29, 4.81.
16. Ramirez-Amador V, Sierra Madero JG, Esquivel Pedraza L et al. Oral secondary syphilis in a patient with human immunodeficiency virus infection. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **81**: 652–4.
17. Ficarra G, Zaragoza AM, Stendardi L, Parri F, Cockerell CJ. Early oral presentation of lues maligna in a patient with HIV infection. *Oral Surg Oral Med Oral Pathol* 1993; **75**: 728–32.
18. Jefferies SDB, Ord RA. An unusual presentation of oral syphilis. *Br J Oral Maxillofac Surg* 1985; **23**: 376–80.
19. Phelps RG, Knispel J, Schuman Tu E, Cernainu G, Saruk M. Immunoperoxidase technique for detecting spirochetes in tissue sections: comparison with other methods. *Int J Dermatol* 2000; **39**: 609–13.
20. Oxford Biotechnology Ltd. ImmunologicalsDirect.com. Product information and data sheet OBT0971, 2002.

Acknowledgements

The authors wish to thank Dr Simon Edwards, Consultant Physician, University College London Hospitals Trust, for help in the interpretation of the clinical histories and serology of cases 1, 2 and 5, Professor Sebastian Lucas, Professor of Histopathology, Kings' College London, for help with the histological diagnosis of case 5, and Miss Philippa Munson, Department of Histopathology, Royal Free and University College London School of Medicine, for undertaking the immunohistochemistry for *T. pallidum.*