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Case report

A non-healing syphilid: Another face of the great imitator

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ABSTRACT

The global re-emergence of syphilis is an exigent public health issue requiring both clinicians and public health practitioners to become familiar with the myriad manifestations of this great imitator. This report describes a case of an originally undiagnosed chronic oral syphilitic chancre, subsequently confirmed by both PCR and immunohistochemistry.

Case report

In early November 2015, a 56-year old heterosexual male was referred from his primary care provider to an otolaryngology clinic in rural Manitoba, Canada, with a 3.5-month history of a small lesion on the inside of his mouth. Over time the lesion expanded with involvement of his left lower lip. He described the lesion as a small ulcer that was tender to touch and irritated by different fluids. It also had a white reticular appearance that could not be wiped away with a Q-tip (Fig. 1A and B). He denied any systemic symptoms including fevers, chills, malaise, night sweats, rash, hair loss, unintended weight loss or dysphagia. The medical history was significant for recent genital herpes simplex virus reactivation, and a remote history of *Chlamydia trachomatis* infection diagnosed in 2011. His recent recurrence of genital HSV coincided with the initial appearance of the oral lesion, but had since resolved. He had a remote tobacco smoking history starting in his teens, 15-year history of smoking marijuana, and his alcohol intake was minimal.

On examination, the patient appeared in a good state of health. There was an irregular, island-shaped, raised, red lesion, 4 cm in diameter (Fig. 1B) with superficial ulceration and weeping on the buccal mucosa adjacent to his lower incisor tooth that was slightly painful to palpation and bled slightly to touch. It extended to the midline of the lower lip. There was no palpable neck lymphadenopathy. The rest of the head and cervical exam as well as review of systems were all unremarkable, specifically with no auditory or ocular complaints. His hematology and biochemistry laboratory testing, including liver enzymes, were all unremarkable. The clinical differential diagnosis at this point in time mainly included: lichen planus, candidiasis, squamous cell carcinoma, and non-hodgkin's lymphoma. Multiple biopsy specimens from the lesions were obtained a week later and sent to Health Sciences Centre, Pathology Laboratory in Winnipeg, Manitoba for histopathological examination.

In mid-November of 2015, a computed tomography (CT) scan of the floor of the mouth as well as head and neck region was also performed. This showed nodular thickening involving the anterior left buccal mucosa and lower lip with multiple enlarged, round, cervical, submental, and submandibular lymph nodes, as well as an enlarged left supraclavicular lymph node and enlarged internal jugular chain lymph nodes. This was suggested to be highly suspicious for buccal mucosal squamous cell carcinoma. The pharynx and larynx appeared within their normal limits.

Histopathological examination showed epithelial hyperplasia with mixed chronic inflammation and exocytosis of inflammatory cells through the epithelium, as well as microabscesses in the superficial dermis (Fig. 1C,D). Special stains to rule out fungal

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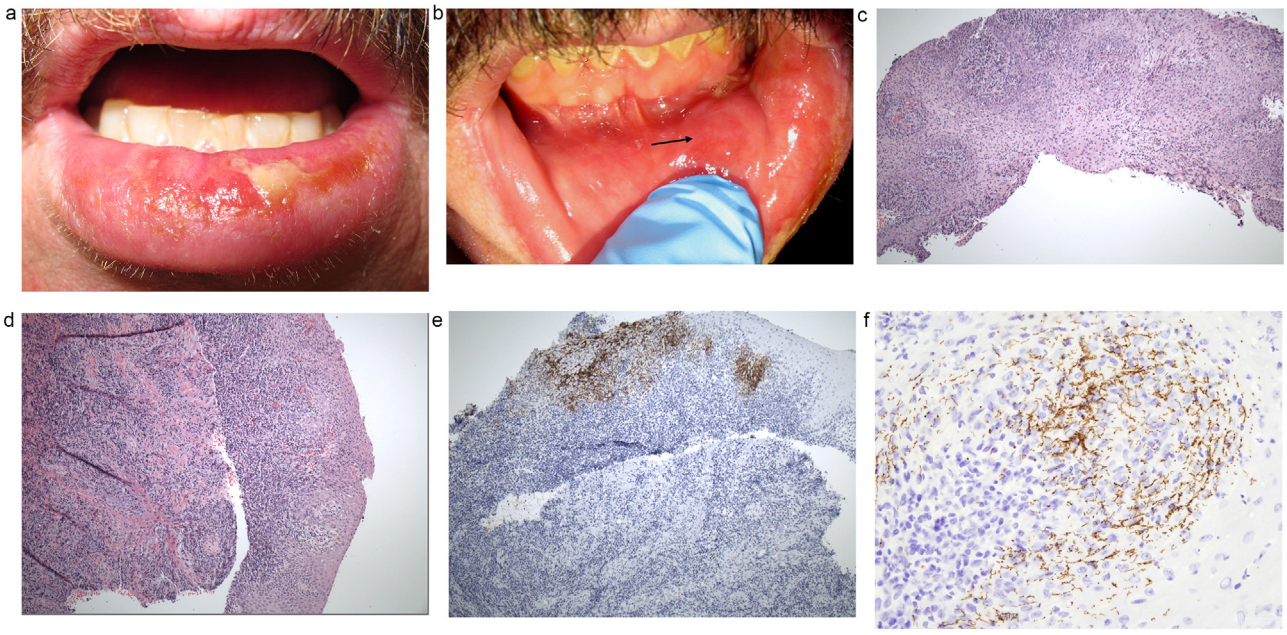

Fig. 1. (A) The lip lesion at the initial presentation in September 2015. Crusted impetiginous lesion with red base. (B) Syphilitic primary chancre on the inside of the left lower lip with red base and indurated margin. (C and D) Hematoxylin & Eosin staining of the lesional biopsies with lymphohistiocytic band-like infiltrate present in the upper part of the dermis that also extends around blood vessels. There is a mixed inflammatory cell infiltrate; however, the plasma cell population is not overly impressive. There is exocytosis of inflammatory cells through the epithelium. (E and F) Immunohistochemistry of the oral biopsy specimens showing slender stained (brown) spirochetes.

organisms were performed and were negative. Staining for treponemes was performed because microabscesses were found and *Candida* was not found. In brief, formalin-fixed, paraffin-embedded tissue sections were stained using purified polyclonal rabbit anti-*Treponema pallidum* IgG (BioCare Medical, Concord, CA) as the primary antibody followed by adding horseradish peroxidase-conjugated anti-rabbit IgG and substrate, per manufacturer's instructions. As shown in Fig. 1E and F, abundant spirochetes stained strongly suggesting infection with *T. pallidum*.

Based on the histopathology results and subsequent notification of public health, further syphilis diagnostic testing was attempted. For direct detection, exudate from the ulcer was obtained on a Dacron swab and sent to National Microbiology Laboratory (NML) in Winnipeg, Canada, in early December of 2015 for syphilis PCR using *tpp47*, *bmp*, and *polA* gene targets as described previously [1]. The above service is routinely offered at NML for direct detection of *T. pallidum* in clinical specimens as previously described in a case of primary syphilis involving the tonsil [2]. In this case, the specimen tested positive for all three gene targets. A serum specimen was collected concurrently and sent to Cadham Provincial Laboratory in Winnipeg, Canada, with the following results: *T. pallidum* antibody tested strongly positive using both Chemiluminescent Microparticle Immunoassay (CMIA, Abbott Laboratories) and *T. pallidum* particle agglutination test (TP-PA; 4+)(Fujirebio). The venereal disease research laboratory (VDRL)(BD Difco™) test was reactive at 1:64 dilution. The patient tested negative for human immunodeficiency virus-1 (HIV-1) p24 antigen plus HIV-1/2 antibody (HIV Combo/4th generation test, Abbott Laboratories); the latter remained negative when retested three months later. A remote negative syphilis serologic test was noted in 2009.

Local primary care and public health staff were subsequently notified of the results and the patient was treated with 2.4 million units of benzathine penicillin G via intramuscular injection in mid December of 2015. Hepatitis B vaccination history was confirmed at this time. Repeat *Chlamydia* and Gonorrhea testing were both negative. Public Health follow-up identified three casual female sexual contacts in the 12-month period prior to the patient's onset of lesion with one reported in March 2015. All three were offered epidemiological treatment with single dose Benzathine Penicillin G and had serologic testing for syphilis on the same office visit. Two were serologically negative for syphilis, but the third contact tested positive (reactive at 1:32 dilution in June 2015). The patient admitted having both oral and genital sex with the latter partner from March through October 2015, but of particular note was that they only used condoms for genital–genital sex. Follow-up VDRL titres showed 16-fold drop in the case patient three months after treatment. On the follow up visit to otolaryngology clinic in January 2016, the lesion had been completely resolved and patient had no other signs or symptoms and did not admit to any symptoms since his first visit in November.

Discussion

Globally, the re-emergence of syphilis has been well-documented in the past decade, especially in industrialized countries with numerous emerging outbreaks reported [3–5]. This requires that clinicians be cognizant of various clinical manifestations of syphilis. Syphilitic mucocutaneous lesions previously known as "syphilids" are salient among protean clinical manifestations of syphilis [6,7]. The infection has four clinical stages: Primary, secondary, latent, and late (tertiary). Primary stage is hallmarked by a solitary mucocutaneous lesion called a chancre. The oral cavity (or buccal mucosa) is the most involved (40–75%) site of extragenital syphilitic lesions [8]. Primary syphilis is mostly associated with regional lymphadenopathy (80%) starting within 10 days after appearance of the lesion(s) [6–8]. During this stage, as opposed to secondary syphilis, there is no generalized lymphadenopathy or systemic signs or symptoms such as fever, malaise, rash, or weight loss.

We had previously reported on a case of primary syphilis in a patient's tonsil with ipsilateral lymphadenopathy and no other signs or symptoms, which subsequently tested positive by both syphilis PCR and serology [2]. Lips tend to be the most commonly affected site in the oropharyngeal cavity during primary syphilis; however, chancres regardless of the body site tend to

spontaneously resolve by 8 weeks after appearance [6–9]. Our patient was unique in having a protracted course of the chancre. When he presented in November of 2015, he reported suffering from the lesion for the previous 3.5 months. During a subsequent interview with public health practitioners, he admitted that one of his sexual encounters was in March; therefore, one plausible explanation would be that he became infected through cunnilingus but due to yet-to-be known factors the primary stage became protracted. The following facts support the notion that this was a primary syphilis case: 1) Solitary lesion: although multiple chancres have been reported in the literature [6–9], a single chancre tends to be the most common manifestation of primary syphilis in immunocompetent hosts; 2) The size of the lesion (4 cm in its greater diameter), its morphology (raised, indurated, with irregular margins and red base and rather white color on top as opposed to smaller, multiple mucosal patches of secondary syphilis with grayish pseudomembrane), and its location in oral cavity (lip); 3) Lack of concomitant systemic/constitutional signs and symptoms as typically seen in secondary syphilis; and 4) The presence of significant regional lymphadenopathy (primary complex) but not generalized lymphadenopathy.

Based on the cornerstone Oslo study, about 10% of untreated patients never develop secondary syphilis [10]. This phenomenon could be due to a combination of the role of pathogenic virulence factors, such as *tprK* gene conversion [11] and/or strong, broadly-reactive oposonophagocytic antibodies in concert with effective $CD8^+$ Th1-mediated adaptive immune responses that may hold the pathogen at bay [12]. Rabbit models of syphilis showed 20% of the animals never developed secondary syphilis in the presence of strong treponemal antibody levels to recombinant p47 antigen as well as VDRL titres similar to those seen in secondary syphilis [11]. Our patient also had very strong treponemal antibody response (CMIA including p47 recombinant antigen) as well as a relatively high VDRL titre.

Conclusion

Although immunohistochemistry is not currently recommended for syphilis diagnosis in non-sterile sites [4,5], positive results with PCR and serology, in conjunction with routine histopathology, are highly suggestive of the diagnosis. This case highlights the need to become more familiar with the numerous faces of syphilis, “the great imitator”, and to consider syphilis in the differential diagnosis of sub-acute and chronic oral ulcers.

Conflict of interest

None declared.

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