Clinico-Pathologic Conference: Case 3

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Clinical Presentation

A 52-year old, HIV+ homosexual male presented to a dental specialist's office with a 3 week history of painful "gum sores" and a white lesion of the right lateral tongue, which appeared 2 weeks after a vacation to the southern United States. General physical exam was unremarkable with vital signs as follows: temperature, 37.1°C; blood pressure, 116/74 mm Hg; pulse rate, 88 beats/min; and respiratory rate, 12 breaths/min. Appropriate medical care, including highly active antiretroviral therapy, had been administered since his diagnosis with HIV 10 years previously. His current regimen included abacavir/lamivudine, ritonavir and atazanavir. During this period, annual rapid plasma reagin (RPR) titers were non-reactive, including the latest testing 8 months prior to lesion onset. The patient indicated that he had been diagnosed and treated for syphilis in 1975, 33 years previously. Recent laboratory reports indicated an undetectable viral load with a CD4 count of 624 cells/mm³.

Oral examination demonstrated prominent fissures of the dorsal tongue with multiple deep, tender, clean-based ulcers (approximately 0.5 cm) exhibiting an irregular, firm, white periphery (Fig. 1a and inset). The patient reported the development of new ulcers at this site over the last 2 days. Asymptomatic non-specific superficial ulcers of the mandibular vestibule (Fig. 1b) and soft palate covered by a

yellow purulent exudate as well as a well-circumscribed, non-removable white plaque (approximately 1.5 cm) of the right lateral tongue (Fig. 1c) were also noted. Slightly tender submandibular lymphadenopathy was observed, with no additional systemic signs or symptoms.

Differential Diagnosis

The differential diagnosis for multiple oral ulcerations in 52-year old, HIV+ homosexual male includes infectious (i.e. bacterial, viral, fungal, protozoal) and idiopathic causes. Fungal and protozoal disease can be reasonably excluded by consideration of the specific clinical features reported. In the absence of any other systemic symptoms and the presence of shallow to slightly deepened ulcers without granularity or a tumor mass-type appearance, deep fungal infections (i.e. histoplasmosis, blastomycosis, coccidioidomycosis) or a protozoal infection (i.e. leishmaniasis) are unlikely considerations. In addition, the latter entity may be reasonably excluded based on lack of travel history to regions endemic for this condition [1]. The WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus diagnostic criteria for oral lesions in HIV infection [2] indicate that the most likely diagnoses include: viral etiologies, reactivation of herpes simplex virus (HSV) and/or cytomegalovirus (CMV); bacterial causes, necrotizing gingivitis/stomatitis or syphilis; or an idiopathic cause, aphthous stomatitis.

Ulcers due to reactivation of HSV are common in immunocompromised patients and while most often affect keratinized mucosa, any oral site may be involved [3]. They often display a scalloped, circinate yellowish/white raised border [3], somewhat distinct from the spike-like irregular, flat border identified in this patient. Histopathologic

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Fig. 1 Initial presentation: The dorsal tongue exhibits fissures and multiple ulcers (a) with an irregular hyperkeratotic periphery (a, inset). The mandibular alveolar mucosa shows three non-specific ulcers (b). A subtle homogenous white plaque of the right lateral tongue was noted (c)

examination, oral cytology, viral culture or serology are necessary to confirm this diagnosis.

Infection with CMV is asymptomatic in the majority of healthy patients, while life-threatening disease may occur in the immunocompromised population. Although uncommon, oral lesions of CMV may manifest as chronic ulcerations with limited additional symptoms [4] as is present in this case. Association with HSV may also occur [4] warranting exclusion of the possibility of a mixed viral infection.

Necrotizing stomatitis is a well recognized ulcerative process occurring in HIV+ patients that may represent extension of bacterial infection of the periodontium into surrounding soft tissues and bone [2]. A characteristic fetid odor and severe pain are commonly reported and the ulcers are often deep-seated [5]. These typical features are absent in the present case, warranting consideration of other possibilities.

Oral ulcerations of the type described in this case could also represent a manifestation of primary or secondary syphilis. Primary syphilitic chancres are classically solitary, clean-based, painless ulcers which most often affect the genitalia and anus. In the context of coinfection with HIV, atypical presentations consisting of multiple painful chancres [6] with an irregular border [7] and oral involvement [7] are more commonplace. In this clinical setting, the oral ulcerations could represent an atypical manifestation of primary disease.

The typical manifestations of secondary syphilis include lymphadenopathy, sore throat, malaise, headache, weight loss, fever, and musculoskeletal pain, along with a cutaneous maculopapular rash. Mucous patches of the tongue, lip, buccal mucosa, and palate may be seen. This patient lacks these typical systemic manifestations expected for secondary syphilis. However, in the HIV-infected population, overlap of syphilitic phases has been documented [7, 8] such that the lesion of the lateral tongue may represent a mucous patch of syphilis occurring concomitantly with persistent primary disease. Though recent RPR titers were negative, a detailed history of recent sexual activity, and repeated serologic testing would be helpful to exclude this possibility.

Aphthous ulcerations of all three subtypes (major, minor and herpetiform) are common in HIV infected patients. They may be of new onset and are often located on the soft palate, tonsils or lateral/ventral tongue [9]. The classic appearance is that of a shallow, round/oval or slit-like ulcer with an erythematous halo. The ulcers in this patient lacked this distinctive appearance and predominated on the dorsal tongue, a distinctly uncommon site for this lesion [9], precluding this as a likely diagnosis.

Diagnosis and Discussion

Cytologic examination of the dorsal tongue and the vestibular ulcers was performed with a provisional diagnosis of herpes simplex infection. When cytologic findings were negative, serologic investigations were initiated to definitively exclude herpetic infection and to evaluate for syphilitic disease. HSV culture media was not available in the dental office and herpes was not identified on cytology, so antiviral therapy was not initiated, pending serologic

studies. Herpes simplex IgM was negative while RPR (1:256 dilution) and fluorescent treponemal antibody absorption were reactive. In addition, using a non-commercially available PCR-based analysis (Center for Disease Control and Prevention, division of Sexually Transmitted Disease Prevention), specific for pathogenic treponemes [10], *T. pallidum* was identified in the scrapings from both the dorsal tongue and the mandibular vestibule.

Upon discussion of the results with the patient, he stated he performed fellatio with a male prostitute during his recent vacation. Five days after a single administration of Benzathine penicillin G 2.4 million units IM, the oral ulcers (Fig. 2a, b) and lateral tongue lesion (Fig. 2c) were virtually resolved. After 7 weeks, the RPR titer was

reduced by three dilutions (1:32) and at 1 year by four dilutions (1:16).

Interestingly, the white lateral tongue lesion may have represented a mucous patch of secondary syphilis, though histologic material was not obtained due to the rapid resolution of the lesion (Fig. 2c). Oral hairy leukoplakia and oral candidiasis, characteristic lesions observed in HIV+ patients, were excluded based on the patient's functional immune status and response to antibiotic therapy.

Syphilis has made a recent resurgence in the HIV infected population, particularly for men having sex with men (MSM) is well documented. The potential for accelerated disease progression in this population underscores the need for early diagnosis; a goal which may be hindered by the atypical clinical presentation of syphilis in patients co-infected with HIV [6]. For instance, up to nearly one-third of patients with primary syphilis do not present with a classic indurated, clean-based, painless ulcer [6]; atypical chancres may be characterized by an irregular border [7] and pain [6]. In addition, multiple chancres, chancres which persist during secondary disease [7, 8], and oral involvement are more commonplace in the HIV-infected population [7]. While the depth and induration of the dorsal tongue ulcers in this case were suggestive of chancres, the presence of multiple irregular, painful lesions was unusual, requiring confirmation with serologic studies.

Risk factors for oral manifestations of syphilis have not been studied, but the patient described had multiple sexual partners, had performed fellatio with a male prostitute and had another sexually transmitted disease (i.e. HIV). Atypical manifestations of syphilis are not known to be associated with one type of syphilis (i.e. primary, secondary) more than another, but they have been noted more often where there is evidence of previous infection [8]. Coupled with the patient being HIV+, the history of syphilitic disease decades earlier, may provide an explanation for the unusual clinical appearance in this case.

This case highlights the resurgence of syphilis in the HIV-infected, MSM population and photodocuments an atypical oral presentation not often depicted in the literature. Additionally, it is a reminder that when unusual clinical manifestations inconsistent with other diagnostic entities are observed, the “great imitator” should always be considered in the diagnostic work-up.

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Fig. 2 Two weeks from initial presentation, 5 days after administration of penicillin G benzathine: Near complete healing of the ulcers of the dorsal tongue (a) and mandibular vestibule (b) is observed. The white plaque of the right lateral tongue is completely resolved (c)

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