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SYPHILIS: CASE REPORT AND UPDATE FOR DERMATOLOGISTS

Case Report: An otherwise healthy 26-year-old woman presented with a one-month history of oval ulcers on the tongue and red-brown scaly papules on the palms, soles, trunk and arms ***(Figure 1).*** She did not recall a history of genital ulceration and did not have systemic symptoms. She had initially been diagnosed with hand, foot and mouth disease by her primary care physician but the eruption persisted prompting a referral to dermatology. She reported one regular male sexual partner for the past several years.

Based on clinical suspicion, syphilis serology was ordered and skin biopsy was performed on a palmar lesion. The *Treponema pallidum* enzyme immunoassay (EIA) was reactive, and the rapid plasma reagin (RPR) was positive at 1:128. HIV testing was negative. Skin biopsy revealed a lichenoid and perivascular dermatitis, with positive immunohistochemical stain for spirochetes, consistent with the clinical and serologic diagnosis of secondary syphilis. She was treated with 2.4 million units of intramuscular benzathine penicillin G at the British Columbia Centre for Disease control. Sexual partners were traced and notified.

Epidemiology

The incidence of syphilis has increased over the past two decades. In Canada, the rate of infectious syphilis (primary, secondary and early latent stages) increased 85% between 2010 and 2015, with the highest rates occurring in British Columbia, Nunavut, and Manitoba[1]. Similar rates of increase are reported in other developed countries such as the United States, Australia, and the United Kingdom[1].

The highest rates of syphilis are observed in men. HIV-positive men who have sex with men (MSM) are disproportionately affected. In Canada, the overall incidence of syphilis is > 300 times greater in HIV-infected MSM compared to the general male population[2]. This is particularly concerning because infection with syphilis increases the likelihood of both transmitting and acquiring HIV, and is associated with increased HIV viral loads[3].

There are several reasons for the rise in syphilis in MSM. Advances in HIV treatment as well as the more recent widespread uptake of pre-exposure prophylaxis for HIV have resulted in a more optimistic risk perception about HIV among MSM. This so-called "HIV optimism" has lead to an increase in risky sexual behaviours, decreased condom use, and a rise in sexually transmitted infections (STIs)[4] . Other behaviours implicated in the rise in STIs among MSM include serosorting (unprotected sex in partners with the same HIV status), and meeting sexual partners via online dating applications[5,6].

Interestingly, there has been a disproportionate increase in the incidence of syphilis compared to other STIs, which cannot be explained by changes to norms and behaviours. Between 2005 and 2014, cases of infectious syphilis in British Columbia rose 90%, compared to a 40% rise in chlamydia and 64% rise in gonorrhea over the same time period. The majority of these cases occurred in HIV-positive MSM, which has led to the hypothesis that antiretroviral therapy may impair anti-treponemal immunity by downregulating both the innate and acquired immune responses to *T. pallidum*, but this hypothesis remains untested[7].

Despite the marked male predominance, the incidence of syphilis is also steadily increasing among women. Along with this, there has been a rise in the incidence of congenital syphilis[7]. Heterosexual transmission of syphilis in both men and women is associated with use of illicit drugs, particularly methamphetamines and injection drugs[8]. The patient in this case did not have any of the above risk factors, reinforcing the importance of considering syphilis in the differential diagnosis in all patients, regardless of demographics.

Clinical Presentation

The primary, secondary and early latent phases of syphilis are highly infectious and timely intervention is important in limiting the spread of infection. The signs and symptoms of untreated primary and secondary syphilis will resolve spontaneously as the infection progresses to the latent phase. If these stages go unrecognized this puts the patient at risk for development of tertiary syphilis, which can affect the cardiovascular system, bone, skin (noduloulcerative or gummatous lesions) and other organs. There is risk of developing neurologic, ocular or otic involvement at any stage of infection[9].

Although most dermatologists would include syphilitic chancre in the differential diagnosis for a solitary, painless genital ulcer, less common presentations may pose a diagnostic challenge. Chancres may be multiple, may present at less common sites (fingers, nipples, and both keratinized and mucosal surfaces of the oral and anogenital areas), and early chancres may present as papules prior to ulcerating[10].

Up to to 97% of cases of secondary syphilis involve skin or mucosa, and the clinical presentation is highly variable. The skin findings may occur with or without lymphadenopathy and systemic symptoms[11]. This case serves as a reminder of some of the classic morphologic features of secondary syphilis. The erythematous papules on the palms and torso demonstrate a typical collarette of scale (Biett's collarette). The oral lesions have the characteristic morphology of mucous patches, which present as well-demarcated oval shaped plaques, erosions or shallow ulcers, with a raised border and white–grey membranous surface. Mucous patches may also involve the buccal mucosa, lips and oral commisures ("split papules"). However, nearly any morphology may occur including psoriasiform, annular, lichenoid, nodular eruptions, leukoderma and patchy nonscarring alopecia among

a long list of less common presentations[9].

New clinical variants of syphilis continue to be described. An urticarial vasculitis- like variant was recently reported, in an HIV-negative individual. This patient had urticarial plaques persisting beyond 24 hours and complement and fibrinogen deposition around the blood vessels and at the dermo-epidermal junction. Immunohistochemical stain for spirochetes showed marked invasion of treponemes into the epidermis[12]. Secondary syphilis can mimic pemphigus vulgaris, both clinically and histologically[13]. Another report describes hemorrhagic crusting of the lips and a diffuse pustular eruption on the trunk, in an HIV-positive individual with secondary syphilis[14]. These presentations place syphilis on the differential diagnosis for bullous or pustular drug eruptions, immunobullous disorders, and other bacterial and viral infections such as impetigo and varicella. Importantly, syphilis can present with atypical cutaneous findings in HIV-positive individuals, which should raise the clinical index of suspicion for syphilis and decrease threshold for syphilis testing in this population.

Diagnostic Testing

Although the specifics of syphilis testing differ between provinces, most laboratories in Canada have adopted a reverse-sequence testing algorithm[15]. This algorithm involves using an automated initial screening test (eg. EIA or chemiluminescence immunoassay; CIA) to detect the presence of anti-treponemal IgM and IgG antibodies. Once reactive, treponemal tests generally remain reactive for the lifetime of the patient, although there is a low rate of sero-reversion if the infection is treated early in the primary stage[16].

All specimens with positive screening treponemal tests then undergo a non-treponemal test (most commonly the RPR). The non-treponemal test is used for staging, monitoring response to treatment, and determining reinfection. The RPR measures antibodies against cardiolipin, which are formed by the host in response to lipoidal material released from damaged host cells, providing a rough indicator of disease activity[16]. This is why the RPR may also be positive in many other conditions, including chronic inflammatory diseases, other infections, pregnancy and injection drug use. False negative non-treponemal tests can also occur, early or late in infection, and rarely in cases where very high antibody concentration interferes with the mechanism of the test (the prozone phenomenon)[9].

Finally, a highly specific treponemal test (such as the Treponema pallidum particle agglutination test; TPPA or the fluorescent treponemal antibody absorption test; FTA-Abs) may be done as a confirmatory test[16]. In some provinces this is done routinely on all samples, and in others it is done only if there is discordance between the treponemal and non-treponemal test results[15].

There is a risk of false negative serology in early syphilis, prior to development of antibodies. Therefore, if clinical suspicion for early syphilis is high but serology is negative, the test should be repeated in 2- 4 weeks[15]. Skin biopsy with immunohistochemical staining using antibodies against treponemal antigens can be a useful diagnostic tool in this situation. These stains are much more sensitive and specific than previously used silver stains such as Warthin-Starry[11]. Additionally, *T. pallidum* can be directly detected by PCR on swabs of lesional exudate from chancres or by darkfield microscopy. However, practical considerations (ie. availability of the test or swabs) may limit the usefulness of these tests in the dermatology clinic setting.

Successful response to treatment is measured by both clinical improvement and a reduction in non-treponemal test titres. The RPR is repeated at specified intervals following treatment, which vary based on the stage of syphilis and comorbidities. In patients successfully treated for syphilis, the non-treponemal tests will usually eventually become nonreactive[16]. Interpretation of syphilis testing can be complex. Diagnosis and management cannot be based solely on current serologic testing. Results need to be

interpreted in the context of both clinical and serologic history to determine whether the case is new or previously treated, and if new, what stage. Because of this complexity and the need for partner tracking and notification, management of syphilis is best done in coordination with infectious disease specialists and public health services.

Conclusion

The resurgence of syphilis is concerning from both an individual patient and public health perspective. By developing an awareness of the protean mucocutaneous manifestations, and a maintaining degree of clinical suspicion, dermatologists have an opportunity to contribute to the control and elimination of infectious syphilis.

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FIGURES

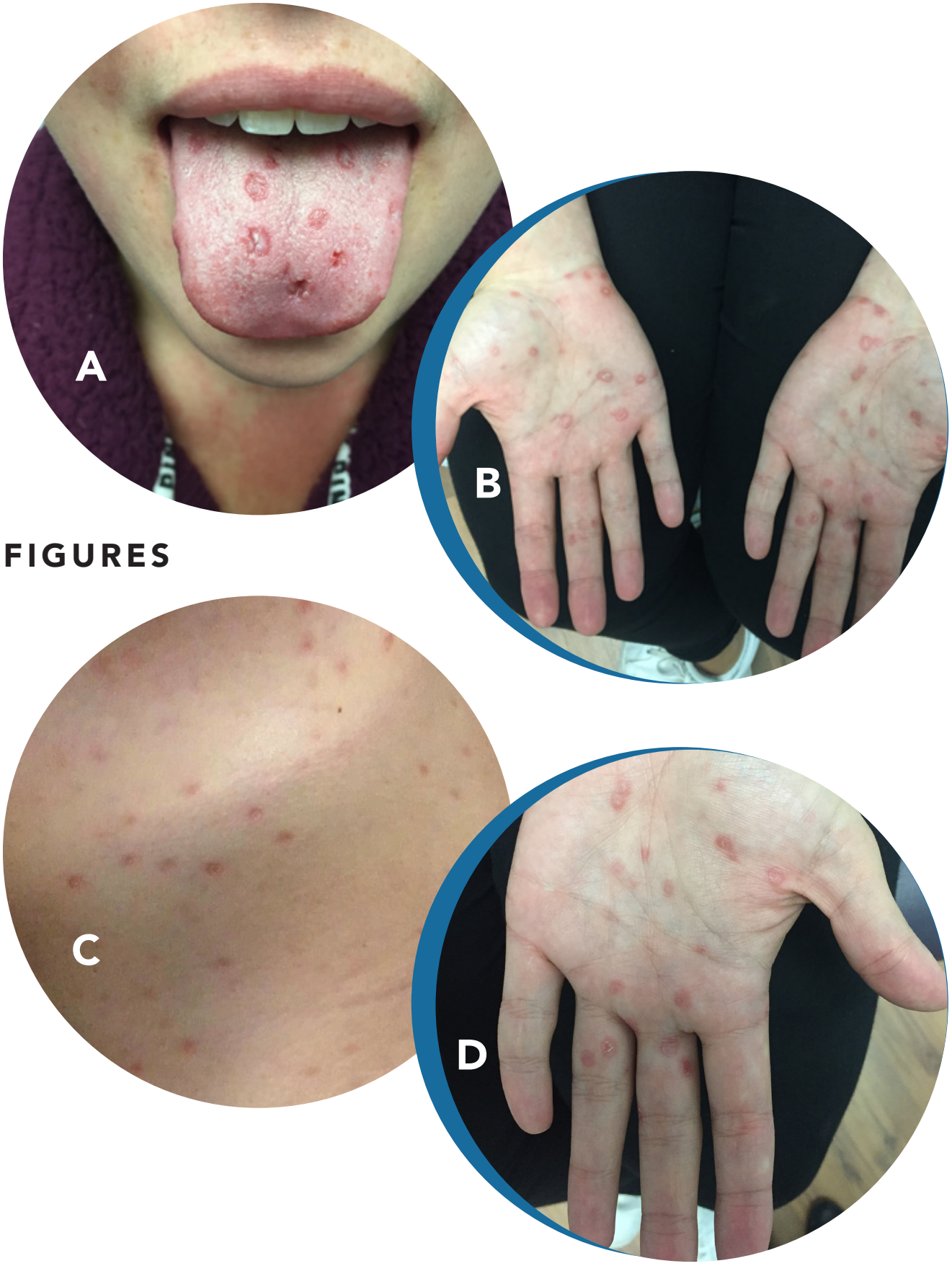

Figure 1: Clinical images of secondary syphilis. A) Mucous patches on the tongue.

B, C &D) Erythematous papules with characteristic collarette of scale on the palms and trunk.