LETTER TO THE EDITOR

Extragenital Chancre in Men Who Have Sex with Men: Six Cases from China

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Introduction

Syphilis is a chronic systemic infectious disease caused by Treponema pallidum via sexual contact (Peeling et al., 2017). The chancre is the main manifestation of the primary stage of syphilis, which often occurs 2–4 weeks after unprotected sexual intercourse. Furthermore, 95% of the chancre occurs in the genital areas (Yu et al., 2012); both clinicians and patients easily ignore extragenital, thus delaying diagnosis and treatment. This Letter reports six cases of extragenital chancre in Chinese men who have sex with men, which was confirmed by medical history, clinical manifestations, histopathological examination, and specific and nonspecific Treponema pallidum antibody tests (rapid plasma reagin test and traditional treatment of syphilis).

Patient 1: Syphilitic Chancre of the Finger

A 36-year-old man who had sex with men (MSM) was presented to our department with an ulcerative lesion of the left index finger that had been left untreated for 6 weeks. The patient’s information is shown in Table 1. The patient reported slight erythema and “breach,” with a little tingling and no other evident discomforts, and no special treatment was administered. Since then, the wound rapidly expanded, with exudation but no obvious pain. Half a month prior, he was treated in a private clinic. It was considered an “atypical mycobacterial infection” and a “skin and soft tissue infection.” For 5 days, he was orally administered clindamycin and topical ichthyol ointment. There was no obvious effect, and the ulcer gradually worsened. Ten days later, he discovered that the axillary lymphadenoma on the same side was large and slightly painful. He has been working in Shenzhen, China, without visiting the COVID-19 epidemic area. There was no history of the same finger, erythema, and blister in the external genitalia, anus, and other parts of the body. Physical examination: a broad bean-sized lymph node could be touched in the left armpit, which was movable and slightly tender. Dermatological condition: a round ulcer with a diameter of 1.1 cm could be seen on the radial side of the end finger joint of the left index finger near the nail edge. The boundary was clear, and the edge was slightly raised; blood seepage and a few thin secretions could be seen at the base. The ulcer was slightly hard and tough with slight tenderness. There were circular scales around the ulcer, but no satellite focus was present (Fig. 1A). No abnormality was found in the genitalia, and no obvious papules, erythema, nodules, and erosion were found in the skin or other body parts. Laboratory examination and results are shown in Table 2. Diagnosis: Primary syphilis and extragenital chancre. Treatment: Benzathine penicillin (2.4 million units) was injected intramuscularly once a week for 3 weeks. After a week of treatment, the ulcer surface was dry; after 2 weeks, the ulcer surface narrowed, and a dark-red scar could be seen on the affected area after 1 month. There was a dark-brown pigmentation spot on the affected area.

Patient 2: Syphilitic Chancre of the Finger

A 34-year-old man was presented with multiple hand ulcers for 3 months. Two months prior, the patient observed a mung bean-sized herpes colliculus on his finger (without any...
conscious symptoms) that gradually enlarged. The patient’s information is shown in Table 1. He was diagnosed with “multiple suppurative granulomas complicated with infection” in a local hospital and was treated with clarithromycin orally and Bactroban ointment externally. However, he felt that there was no obvious effect. He came to our hospital for further diagnosis and treatment. He denied a history of vulva and perianal ulcers before onset and reported no discomfort, such as fever, sore throat, and painful urination. The patient was married, gay, and has no regular sexual partner. He had multiple unprotected sexual contacts in a homosexual massage parlor and often used the hand massage “customer”

| Information                  | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Age                          | 36        | 34        | 45        | 27        | 18        | 42        |
| Course of the disease (weeks)| 6         | 12        | 4         | 4         | 8         | 6         |
| Clinical diagnosis           | Non-TB infection | Pyogenic granuloma | Oral ulcer | Oral ulcer | Oral ulcer | Skin ulcer |
| Place of the chancre         | Finger    | Finger    | Left buccal mucosa | Lower lip | Lower lip | Left chest |
| Number of the chancre        | 1         | 3         | 1         | 1         | 1         | 1         |
| Any other manifestations of syphilis | No       | No       | Secondary syphilis rash; plum hair loss | No       | No       | No       |
| Condoms                      | Yes       | Yes       | Yes       | No        | No        | Yes       |
| Possible nodes of infection  | Masturbation | Masturbation | Oral sex | Oral sex | Oral sex | Biting nipple |
| Sex worker                   | Yes       | Yes       | Yes       | No        | No        | No        |
| Multiple sexual partners     | Yes       | Yes       | Yes       | No        | Yes       | Yes       |
| Sex drug                     | No        | No        | Yes       | Yes       | No        | No        |
| Addictive drug               | No        | No        | No        | Yes       | No        | No        |
| Commercial sex               | No        | No        | No        | Yes       | Yes       | Yes       |
| Married                      | No        | Yes       | Yes       | No        | No        | Yes       |
| Sexual orientation           | Gay       | Gay       | Gay       | Bisexual  | Gay       | Gay       |

Fig. 1 Dermatological examination of syphilitic chancre on the finger. **A** Patient 1; **B** Before the second patient’s treatment; **C** After the third patient’s treatment

| Laboratory examination                  | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|-----------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Haemophilus ducreyi (microscopy)        | −         | −         | −         | −         | −         | −         |
| Bacterial culture                       | −         | −         | −         | −         | −         | −         |
| HSV-DNA                                 | −         | −         | −         | −         | −         | −         |
| Treponema pallidum (Fig. 3C)            | +         | +         | +         | +         | +         | +         |
| TPPA 1:640                               | 1:1280    | 1:1280    | 1:8       | 1:1280    | 1:640     | 1:1280    |
| HIV                                     | −         | −         | −         | +         | −         | −         |
| Before treatment the RPR                | 1:32      | 1:16      | 1:16      | 1:8       | 1:8       | 1:64      |
| After treatment RPR 1 month             | 1:2       | 1:4       | 1:2       | 1:4       | 1:4       | −         |
| After treatment RPR 2 months            | −         | −         | −         | −         | −         | −         |
| After treatment RPR 3 months            | −         | −         | −         | −         | −         | −         |
| After treatment RPR 6 months            | −         | −         | −         | −         | −         | −         |
genitalia, anus, and anal perianal. Dermatological examination: Two ulcerations were present at the flexion of the right middle finger near the metacarpal joint, and one ulceration was observed at the tip of the left middle finger. Both were round, soybean-sized, with a clear boundary surrounded by a dike, brown in the center, hard and tough feeling when touched, slightly moist on the surface, and some serous ooze after extrusion. There were no obvious erythema, papules, nodules, and erosion in other body parts. Multiple broad bean-sized, medium-hard, movable, nontender lymph nodes could be palpated under both armpits (Fig. 1B). Laboratory examination and results are shown in Table 2. The patient refused histopathological examination. According to history, clinical manifestation, and syphilis serological examination diagnosis, syphilis (multiple hard chancres: ulcus durum of fingers) was implicated. Treatment: Benzathine penicillin (2.4 million units) was administered intramuscularly, divided into two buttock muscle injections, once a week, three consecutive times. Follow-up: After 2 weeks of treatment, the ulcer became soft. After 4 weeks, it became crusty and completely shed, leaving erythema and slight desquamation (Fig. 1C).

Patient 3: Syphilitic Chancre of the Lip

A 45-year-old man was presented with a buccal mucosa ulcer and foreign body sensation for a month. One month prior, he observed a soy bean-sized hard tubercle in the buccal mucosa, with foreign body sensation but without pain or other discomforts. The patient’s information is shown in Table 1. He purchased and orally administered cephalosporin antibiotics by himself, but no obvious effect was observed. The rash was significantly enlarged, with yellow secretions on the surface. Since the onset of the disease, there has been recurrent fever, with the highest temperature reaching 38.5 °C. The lymph nodes behind the mandible and ears were enlarged without pain. He denied a history of extragenital and oral ulceration, local bite, and scald. The patient was homosexual, had several homosexual acts, and with a history of cunnilingus and oral sex. Systematic examination: Bilateral submandibular and retroauricular lymph nodes were enlarged to soybean-sized, with good activity and no evident tenderness/pain. Other systematic examinations revealed no abnormalities. Dermatological examination: there was a dime-sized, erosive ulcerative lesion on the left buccal mucosa, which was firm and touched with a clear boundary. A few purulent secretions could be observed on the surface, which was grayish-white membranous with red surroundings (Fig. 2A). When the secretions were removed, dike damage was visible but without tenderness or pain. Slight erythema could be observed all over the body, ring-like scaly erythema could be seen in the metacarpal and plantar parts, and insect erosion alopecia could be observed in the occipital and temporal parts. Laboratory examination and results are shown in Table 2. Diagnosis: Oral mucosal chancre, secondary syphilis rash, and plum toxicity alopecia. Treatment: Benzathine penicillin (2.4 million units), administered intramuscularly, divided into two buttock muscle injections, once a week, two consecutive times. The ulcer surface healed 3 weeks later, and no recurrence has been observed so far.

Patient 4: Syphilitic Chancre of the Lip

A 27-year-old Chinese man was presented to our clinic with a mucous ulcer of the lower lip for more than 1 month. The patient observed a mung bean-sized papule on the lower lip mucosa more than 20 days prior without obvious discomfort. The patient’s information is shown in Table 1. The surface of the papule appeared ulcerated and swollen, and there was a burning sensation after being stimulated by hot and spicy food. He went to the outpatient department for the treatment of an “oral ulcer” and was treated with vitamin C and metronidazole tablets orally and chlorbitine to gargle. After administration for several days, there was no obvious effect, and the ulcer and swelling gradually enlarged. He denied a history of oral ulcer, local bite, scald, or external genital ulcer. A month prior, he had homosexual contact and oral sex. Systematic examination: Cervical and submaxillary lymph nodes were not felt or swollen, and no abnormalities were observed before the systematic examination. Dermatological condition: The lips were dry and desquamated, with an obvious broad-sized swollen ulcer on the lower lip mucosa near the right corner of the mouth, having a hard texture and lacking normal mucosa softness. The surface was dry and red without obvious exudation or abnormal tenderness/pain (Fig. 2B). Laboratory examination and results are shown in
Table 2. Diagnosis: Chancre. Treatment: Benzathine penicillin (2.4 million units), administered intramuscularly, divided into two buttock muscle injections, once a week, two consecutive times. Three weeks later, the ulcer surface healed, a local white scar was left, and no recurrence has been observed so far.

**Patient 5: Syphilitic Chancre of the Lip**

An 18-year-old man was presented to our hospital with a 2-month history of lower lip mucosal ulcer. He accidentally observed a small papule on the lower lip without obvious discomfort 2 months prior; then, it appeared ulcerated and enlarged on the surface. The patient’s information is shown in Table 1. He was diagnosed with an “oral ulcer” and treated with an unknown medicine. He denied a history of oral ulcer, local bite or scalding, and external genital ulcer. The patient was homosexual and had a history of acquired immunodeficiency syndrome (AIDS) (he was taking anti-AIDS drugs). Dermatological condition: There was a broad bean-sized edema ulcer on the lower lip, which was as hard as rubber when touched. The surface was dry and crusting without exudation, and there was redness around it but without any tenderness or pain (Fig. 2C). Laboratory examination and results are shown in Table 2. Diagnosis: Extragential chancre. Treatment: Benzathine penicillin (2.4 million units), administered intramuscularly, divided into two buttock muscle injections, once a week, two consecutive times. The ulcer surface healed 3 weeks later, and there has been no recurrence during follow-up.

**Patient 6: Syphilitic Chancre of the Nipple**

A 42-year-old man was presented to our hospital with a papillary ulcer of 1.5-month duration. He observed a small ulcer on his nipple 6 weeks prior, which gradually enlarged. He was diagnosed with “skin ulcer-related enquiries” in the local hospital and was administered Bactroban ointment externally, but with no obvious curative effect. The patient’s information is shown in Table 1. The patient denied a history of vulva and perianal ulcers before onset and had no discomfort, such as fever, sore throat, and painful urine. Dermatological examination: There was a crater-like ulcer on the left nipple, which was round, well-defined, and surrounded by a dike. A scab and a few secretions were observed in the center of the skin lesion with hard and tenacious touch. There was no obvious erythema, papule, nodule, or erosion observed in other body parts (Fig. 3A). Laboratory examination and results are shown in Table 2. According to the medical history, clinical manifestation, and syphilis serological examination, syphilis (extragenital chancre of the nipple) was implicated. Treatment: Benzathine penicillin (2.4 million units), administered intramuscularly, divided into two buttock muscle injections, once a week, three consecutive times. Follow-up: After 2 weeks of treatment, the ulcer became soft, and 4 weeks later, the ulcer became crust and completely shed, leaving erythema and slight desquamation (Fig. 3B).

**Discussion**

Syphilis is a chronic bacterial infection caused by *Treponema pallidum* (Hook, 2017). According to the latest estimate of the World Health Organization, in 2012, approximately 17.7 million individuals aged 15–49 years suffered from syphilis, with an estimated 5.6 million new cases yearly (Newman et al., 2015). The incidence and prevalence rate of syphilis vary from region to country, but data show that syphilis has a high incidence rate among MSM. Syphilis is related to high-risk sexual behavior, which greatly increases the transmission and acquisition of the AIDS virus (Hook, 2017). The literature reports that the number and proportion of syphilis cases reported in the MSM population in the USA and Western Europe have been increasing since 1998 (Abara et al., 2016). In 2015, the incidence rate of primary and secondary syphilis among MSM in the USA (30.9%) was 221 times that of women (1.4%) and 106 times that of heterosexual men (2.9%). In Canada, the incidence rate of HIV
positive MSM patients is 300 times higher than that reported in the general male population (Burchell et al., 2015). In the past 30 years, with the change of the Chinese understanding and attitude toward sex and sexual behavior and the gradual diversification of sexual behavior, the incidence rate of sexually transmitted diseases has significantly increased. Nevertheless, the incidence of syphilis in China is increasing at an annual rate of 16.3% (Yang et al., 2017). MSM also have a high rate of syphilis (Ruan et al., 2009).

Chancroid is the main manifestation of the skin lesions of primary syphilis, which often occurs 2–4 weeks after unprotected sexual contact. The typical damage is characterized by the surrounding dike-like uplift, flat base, flesh red, a small amount of serous exudate on it, and cartilage-like hardness when touched. More than 95% of the hard chancre occurs in the genital area (Yu et al., 2012), and in the male pudendal chancre, the prone parts are the coronal sulcus, glans, penis, foreskin, or urethral orifice. MSM may lead to atypical clinical manifestations of patients with primary syphilis due to having multiple sexual partners at the same time, multiple forms of sexual activity without condom use (anal sex, oral sex, fist sex), and other factors. Its damage can also occur in the tonsils, tongue, lips, fingers, nipples, areola, and eyelids, in addition to the genitals, anus, and rectum (Chiu & Tsai, 2012; Ma & Vano-Galvan, 2013). Although the clinical characteristics of genital and extragenital chancre are similar (ulcerative, sclerosing painless nodule lesions, and accompanied by local adenosis), the lesions of extragenital chancre (ulcerative, sclerosing painless nodule lesions, and accompanied by damage to the eyes, external genitalia, and other parts, nodular erythema, migratory arthritis, acupuncture reaction (+), syphilis serum reaction (−)) (Nakamura et al., 2020). (4) Behcet’s disease: deep ulcer, no hard chancre, accompanied by damage to the eyes, external genitalia, and other parts, nodular erythema, migratory arthritis, acupuncture reaction (+), syphilis serum reaction (−) (Franco-Paredes et al., 2018).

(3) Tuberculous ulcer: history of tuberculosis, ulcerous deep concave, marginal rat-like phagocytosis, chest X-ray showing tuberculosis (Franco-Paredes et al., 2018). (4) Behcet’s disease: deep ulcer, no hard chancre, accompanied by damage to the eyes, external genitalia, and other parts, nodular erythema, migratory arthritis, acupuncture reaction (+), syphilis serum reaction (−) (Nakamura et al., 2020). (5) Mucous patches of secondary syphilis: Diffuse mucosal patches appear in the oral cavity 7–20 weeks after syphilis infection, mostly distributed on the inner surface of lips and cheeks or tongue, pharynx, tonsil, and throat, causing redness and swelling. Shallow erosion: Round, flat, or slightly high, covered with gray-white exudate, with a red halo at the edge and no pain (Smith et al., 2021). It should also be differentiated from soft chancre, herpes simplex, mycosis, cytomegalovirus infection, autoimmune diseases (pemphigus, pemphigoid), immune-related diseases (lichen planus, drug-related manifestations), and oral cancer or precancerous lesions (mucosal leukoplakia, squamous cell carcinoma, non-Hodgkin’s lymphoma).

Chancres may be chapped or erosive due to being played with, stimulated, and bitten by sexual partners with clear boundaries. The chancre occurring in the nipple should be differentiated from Paget’s disease of the breast, eczema of the nipple, herpes simplex virus infection, erosive adenomatosis of the nipple, basal cell carcinoma of the nipple, leishmaniasis, melanoma, and skin lymphocyte proliferation (Podlipnik et al., 2015; Sim et al., 2010; Yu et al., 2012).

The chancre of the finger may not be characterized by a typical painless ulcer but rather nonulcerative invasive isolated plaque. It is often misdiagnosed as furuncle, herpetic gangrene, postular ulcer, suppurative granuloma, milker’s nodules, sheep pox, anthrax, sores, and chancroid pyoderma (the superficial ulcer of the disease is quite similar to syphilitic hard chancre and easily confused). Basal cell and squamous cell carcinoma must also be distinguished (López-Jiménez et al., 2021; Palfi et al., 2008).

The transmission route of extragenital chancre is the same as that of the genital chancre. Therefore, it is speculated that this part may be infected due to contact with saliva or body fluid containing Treponema pallidum. In the cases reported in this Letter, we found that the patients with finger chancre were sex workers and had a history of unprotected contact with customers’ genitals and anus many times in same-sex massage places and oral sex history of chancre in the oral cavity. Patients with chancre have a history of nipple damage caused by multiple kissing and biting.

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If the patient is infected with syphilis, clear diagnosis by the hospital, and timely treatment, this can reduce the infectivity and be cured. However, because of the following reasons, it often leads to missed diagnoses and misdiagnosis:

1. The discrimination against MSM in Chinese traditional social ethics persists; MSM must hide their identity, and the community activities are hidden, which has formed a stubborn psychological barrier to self-protection and significantly reduced their medical demands. (2) The clinical manifestations of syphilis in various stages are diverse, and they are often called “the great simulator” (Bissessor & Chen, 2009).

Due to the atypical clinical manifestations of MSM patients with primary syphilis, it is easy to be missed and misdiagnosed. Therefore, we should be vigilant for simple, painless ulcers, especially lips, tongue, breast, fingers, and other parts, and diagnose syphilis and carry out plump blossom expelling treatment as soon as possible to avoid the occurrence of cardiovascular syphilis, neurosyphilis, and serious complications, which is of great significance to the quality of life of patients. For suspected cases, even if there is no laboratory evidence, syphilis infection cannot be denied, and close follow-up observation should be carried out. Each case should be judged in combination with clinical manifestations, laboratory examination, treatment history, follow-up, epidemiological history, and comprehensive analysis. Simultaneously, according to the characteristics of MSM groups around the country, promoting MSM groups is necessary to establish health awareness and the concept of being responsible for society and individuals, as well as to advocate the use of condoms and to reduce the number of sexual partners in order to promote the change of MSM individuals’ high-risk behaviors.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Ethics Committee of Huazhong University of Science and Technology Union Shenzhen Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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