ORIGINAL ARTICLE

The Great Imitator: Atypical Cutaneous Manifestations of Primary Syphilitic Chancre

Huizi Gong, Mengyin Wu, Jun Li*, Heyi Zheng*

Department of Dermatology and Venereology, Peking Union Medical
College Hospital, Chinese Academy of Medical Sciences &
Peking Union Medical College, Beijing 100730, China

Key words: primary syphilis; chancre; misdiagnosis

Objective To analyze the reasons of misdiagnosis of primary syphilitic chancre and strengthen the understanding of atypical features of this disease.

Methods A case series of twenty-seven challenging primary syphilis patients who were not immediately recognized as chancre was included in our study. The clinical data including the patients' age, sex, skin lesions, HIV status, syphilis serologic test results, treatment, and follow-up results were collected. Hematoxylin-eosin and immunohistochemistry staining of skin biopsy sections were reviewed.

Results Four female cases with extragenital chancres presenting as erythema or erosive skin lesions on the nipple were misdiagnosed as Paget's disease or eczema. The disorder of missed or misdiagnosed male cases manifested as syphilitic balanitis or multiple chancres on the penis root and adjacent pubis rather than coronal sulcus or frenum. Patients with nonreactive nontreponemal tests at initial presentation were also easily missed or misdiagnosed.

Conclusion Primary syphilis presenting as multiple lesions rather than a single chancre, at atypical locations, or with a nonreactive nontreponemal test result, tends to be missed or misdiagnosed.

SYPHILIS, a multistage sexually transmitted disease, caused by *Treponema pallidum*, remains a major global health problem. The incidence of syphilis has increased strikingly during the last three decades in China, the average annual increase having been as high as 16.3%.^[1]

According to its infectious course, syphilis can

be divided into three main stages: primary, secondary, and tertiary. If misdiagnosed or left untreated, primary syphilis will progress to secondary and, eventually, tertiary stages.^[2, 3] Thus, diagnosing primary stage of syphilis is important because appropriate treatment can prevent the lesion from developing into secondary, and even tertiary stage, more importantly, reduce the risk of transmission to sexual partners.

Primary syphilis may manifest as atypical chancres or atypical locations. Confirming a diagnosis of chancre is mainly based on serology, as direct diagnosis by dark-field microscopy presents difficulties that limit its widespread use.^[4] However, the results

Received October 5, 2020. Published online October 16, 2021.

*Corresponding author Jun Li, Tel: 86-10-69151502, E-mail: lijun35@hotmail.com; Heyi Zheng, zhenghy62@yahoo.com.cn

Supported by Beijing Municipal Science and Technology Commission (Z191100006619011) and Capital's Funds for Health Improvement and Research (2020-2-4016).

of serologic nontreponemal tests are only positive in 50% of patients with primary syphilis.^[5] Furthermore, false-negative serologic test results have been reported previously in early syphilis/HIV coinfection^[6] and the prozone phenomenon.^[7] Thus, primary syphilitic chancre could be misdiagnosed as other skin diseases by physicians and even by dermatologists.

Here, we describe a series of challenging cases not immediately recognized as chancre. Some cases were suspected as primary syphilis by histopathologic pointers after a skin biopsy was done, and subsequent immunohistochemical staining for *treponema pallidum* and serologic testing finally confirmed the diagnoses. Some cases were confirmed as primary syphilis by direct fluorescence antibody testing. This study presents the clinical aspects that masqueraded chancre and delayed the diagnosis.

PATIENTS AND METHODS

Study population

Medical records of the newly diagnosed primary syphilis cases with chancres initially missed or misdiagnosed as other skin diseases at the Peking Union Medical College Hospital, Beijing, China, between September 2008 and May 2019, were retrospectively reviewed. Cases with incomplete laboratory data [including rapid plasma reagin (RPR) and particle agglutination assay for antibody to *T. pallidum* (TPPA)] and clinical information (including lesion numbers, location, manifestation, initial diagnosis and follow-up results) were excluded. Finally, 27 patients were included. Histologic examination provided key diagnostic clues in some cases and subsequent immunohistochemistry and serologic tests for syphilis confirmed the final diagnoses. Some cases were confirmed as primary syphilis by direct fluorescence antibody testing. Direct fluorescence antibody testing was routinely examined for genital ulcer diseases.

Data collection

The clinical data including the patients' age, sex, skin lesions, HIV status, syphilis serologic test results, treatment, and follow-up results were obtained from the medical record. Hematoxylin-eosin and immunohistochemistry staining of skin biopsy sections were reviewed.

Ethical review

Written informed consent was obtained from all participants. This study was approved by the institu-

tional review boards of the Peking Union Medical College Hospital (reference number S-K653).

RESULTS

Clinical features

A total of 27 patients with chancre who were initially missed or misdiagnosed as having other skin conditions were included. All of them did not receive any treatment before misdiagnosis, and the diagnosis of syphilis was confirmed by both non-*Treponema pallidum* serology test. Clinical features of the 27 cases are summarized in **Table 1**. The female-to-male ratio was 1:2. The age of them ranged from 19 to 58 years. Two patients (Case 12 and 27) were positive for HIV. Coinfection with herpes simplex virus-2 was found in 1 of 6 patients who were tested.

Four female cases (Cases 3, 5, 8, and 16) with extragenital chancres that manifested as erythema or erosive skin lesions located on the nipple (**Figs. 1A, 1B**), were misdiagnosed with mammary Paget's disease or eczema. Eleven missed or misdiagnosed male cases presented with multiple chancres (**Fig. 1C**) or syphilitic balanitis (**Fig. 1D**). Four missed or misdiagnosed male cases presented with lesions located on unusual site: the base of the penis or adjacent pubis (**Figs. 1E, 1F**). Seven missed or misdiagnosed cases presented with nonreactive RPR at initial presentation.

Histological features

The skin biopsy specimen with hematoxylin-eosin staining showed underneath an ulcer, there were densely infiltrated lymphocytes, plasma cells and sparse neutrophils, hemorrhage, and blood vessels lined with plump endothelial cells (**Fig. 2A, 2B**); parakeratosis and pseudoepitheliomatous hyperplasia of epidermis; diffuse infiltration of lymphocytes and plasma cells in the dermis (**Fig. 2C, 2D**). Immunohistochemical analysis for *Treponema pallidum* demonstrated numerous spirochetes in the epidermis and dermis (**Fig. 3A-3D**). Direct fluorescent antibody staining of lesion smears for *Treponema pallidum* identified *Treponema pallidum* based on antigen detection and morphology (**Fig. 4A, 4B**).

DISCUSSION

For patients with syphilis, chancre is usually the first cutaneous lesion, appearing 10–90 (average 21) days after infection. The typical incipient chancre is a

Table 1. Clinical features of the 27 misdiagnosed primary syphilis cases

Case	Sex	Age (yrs)	Clinical diagnosis	Lesion location	Skin lesion	Chancres' duration (weeks)	Chancres' numbers	RPR titer
1	Male	38	Ulcer	Glans	Ulcer	3	1	0
2	Male	57	Paget's disease	Root of the penis	Erosion	6	1	1:8
3	Female	33	Paget's disease	Left nipple	Scaly erythema	12	1	≥1:32
4	Male	48	Paget's disease	Root of the penis	Ulcer	8	1	≥1:32
5	Female	19	Paget's disease	Bilateral nipples	Erosion	8	2	≥1:32
6	Male	36	Ulcer	Glans, scrotum	Ulcer	2	2	1:1
7	Male	58	Behcet's disease	Penis, scrotum	Ulcer	16	3	≥1:32
8	Female	44	Eczema	Left nipple	Erosive erythema	2	1	1:8
9	Male	37	Scabies	Root of the penis	Nodules	12	2	0
10	Female	26	Behcet's disease	Perineum	Ulcer	2	1	1:1
11	Male	32	Balanitis	Coronal sulcus	Erosion	4	Syphilitic balanitis	≥1:32
12	Male	28	Genital herpes	Scrotum	Erosion	1	3	1:4
13	Female	27	Ulcer	Vaginal orifice	Erosion	4	1	0
14	Male	19	Ulcer	Upper lip	Ulcer	4	1	0
15	Female	26	Vaginitis	Cervix uteri	Erosion	6	1	1:32
16	Female	27	Paget's disease	Right nipple	Scaly erythema	6	1	1:16
17	Female	51	Ulcer	Perineum	Ulcer	3	1	≥1:32
18	Male	24	Folliculitis	Pubis	Ulcer	4	4	1:16
19	Male	22	Balanitis	Glans	Erosion	2	1	1:16
20	Male	34	Balanitis	Glans	Erythema	6	Syphilitic balanitis	1:32
21	Male	33	Balanitis	Glans	Erythema	3	Syphilitic balanitis	0
22	Male	35	Balanoposthitis	Glans and foreskin	Ulcer and erosion	2	Multiple	1:8
23	Male	46	Balanoposthitis	Glans and foreskin	Erythema	2	Syphilitic balanitis	1:4
24	Male	42	Ulcer	Prepuce	Ulcer	2	1	0
25	Female	27	Ulcer	Lower lip	Ulcer	6	1	≥1:32
26	Male	56	Balanoposthitis	Glans and foreskin	Erythema	12	Syphilitic balanitis	≥1:32
27	Male	40	Chancroid	Glans	Ulcer	3	1	0

RPR: rapid plasma reagin.

small red papule or crusted superficial erosion. In a few days to several weeks it becomes a round or oval, indurated, slightly elevated papule, with an eroded but not ulcerated surface that exudes serous fluid. On palpation it has a cartilage-like consistency. The lesion is usually, but not invariably, painless. Untreated, the chancre tends to heal spontaneously in 1 to 4 months.

Approximately 5% to 10% of chancres are extragenital.^[8] They affect the lips,^[9] tongue, tonsil, female breast, index finger, and, especially in men who have sex with men, the anus.^[10, 11] In our series, four female cases of extragenital chancres presenting with erythema or erosive skin lesions locating on the nipple was misdiagnosed as mammary Paget's disease or eczema. Nipple chancres should be differentiated from nipple eczema, mammary Paget's disease, herpes simplex infection, erosive adenomatosis of the nipple, squamous cell carcinoma, and nontuberculous mycobacterial infection etc.

Eczema of the nipple is more commonly seen in female adolescents with severe pruritus and in most cases involving bilateral nipples. This disorder tends to have intermittent flare-ups with symptoms worsening rapidly, which can be relieved by using a short course of topical steroids. Mammary Paget's disease predominantly affects postmenopausal women. The main clinical manifestation is a unilateral, chronic ulcerated nipple with serous or bloody discharge. Paget cells (malignant, intraepithelial adenocarcinoma cells, appearing singly or in small groups in the epidermis) are the typical histologic findings. Patients with erosive lesions on the nipple should be asked about his or her sexual history (e.g., a bite during sexual intercourse). Awareness of such unusual presentation can help avoid misdiagnosis of primary syphilis.

Chancres generally occur singly, although multiple chancres may be present in up to 47% of cases and patients with multiple chancres are easily

Figure 1. Macroscopic manifestations of the representative cases.

A. Chancre, erosive skin lesions located on the nipple, misdiagnosed as mammary Paget's disease; B. Chancre, scaly erythema on the nipple, misdiagnosed as mammary Paget's disease; C. Primary syphilis, multiple chancres; D. Primary syphilis presenting as syphilitic balanitis; E. Primary syphilis, multiple chancres on the root of the penis; F. Primary syphilis, multiple chancres on the pubis.

Figure 2. Hematoxylin-eosin staining of the tissues obtained from syphilitic chancres. An ulcer with numerous infiltration of lymphocytes, plasma cells, and blood vessels lined with plump endothelial cells (A, $\times 100$; B, $\times 200$). Parakeratosis and pseudoepitheliomatous hyperplasia of epidermis; an abundance of diffusely infiltrated lymphocytes and plasma cells in the dermis (C, $\times 100$; D, $\times 200$)

misdiagnosed.^[12, 13] In our series, seven patients who presented with multiple lesions were missed or misdiagnosed. *Treponema pallidum* has been implicated as a possible cause of balanitis. Balanitis may be the only

Figure 3. Immunohistochemical staining for *Treponema pallidum* chancre. Many spirochetes (red) in the perivascular area of the dermis (A, $\times 100$; B, $\times 200$); Many spirochetes (red) in the adjacent epidermis of chancre (C, $\times 100$; D, $\times 200$).

Figure 4. Direct immunofluorescence confirming the presence of *Treponema pallidum* in the lesion ($\times 1000$).

clinical expression of primary syphilis. In our case series, five patients presented with syphilitic balanitis.^[14]

Chancres are located on the penis in 99% of heterosexual male patients. The most common penile sites are the coronal sulcus (35%), glans (29%), shaft (22%), prepuce (19%), frenulum (10%) and urethral meatus (1%).^[15] Chancres at the base of the penis and adjacent pubis are rare and associated with the use of condoms. Four men who were missed or misdiagnosed presented with chancre on the root of the penis and adjacent pubis rather than the coronal sulcus and glans.

Nontreponemal tests are positive in only 50% of patients with primary syphilis.^[5] The likelihood of positivity depends on the duration of infection. Seven cases missed or misdiagnosed as having other skin diseases showed nonreactive RPR at initial presentation. Therefore, a negative nonreactive nontreponemal testing results cannot exclude primary syphilis, and further examination of suspicious lesions is needed. Nontreponemal antibody assays such as RPR are less sensitive than treponemal antibody assays (such as FTA-ABS or TPPA) in detecting primary syphilis; hence, for diagnostic purposes the latter would be preferable to the former.

Evidence indicates that immunohistochemical

analysis improves the sensitivity and specificity for detecting *Treponema pallidum*.^[16, 17] Spirochetes primarily reside in the epidermis, except for one report of bacteria around the dermal capillaries. Similarly, in our present study, the spirochetes were detected in the epidermal tissues, sparse to moderate numbers of dermal spirochetes. *Treponema pallidum* was mainly detected in the lower epidermis and the upper dermis, which is consistent with previous studies describing immunohistochemical detection of *Treponema pallidum* in the basal layer.^[17, 18]

All health professionals should bear in mind that a chancre may present in any conceivable morphologic form and may be located on any part of the body except the nails, hair, and teeth. Furthermore, nonreactive RPR is common in primary syphilis. A chancre frequently manifest itself atypically. Chancres are commonly multiple and are occasionally extragenital in location. Such variable presentations and locations have led to missed diagnosis and misdiagnosis.^[15] All physicians, not only dermatologists and sexually transmitted disease clinicians, should be aware that chancre presentation may be atypical in morphology. Although chancre is easily cured, the consequences of missed diagnosis and misdiagnosis can be serious and even life-threatening.

Conflicts of Interest Disclosures

We have no conflicts of interest to declare.

REFERENCES

1. Yang S, Wu J, Ding C, et al. Epidemiological features of and changes in incidence of infectious diseases in China in the first decade after the SARS outbreak: an observational trend study. *Lancet Infect Dis* 2017; 17(7):716-25. doi: 10.1016/S1473-3099(17)30227-X.
2. Ghanem KG, Champion EW, Ram S, et al. The modern epidemic of syphilis. *N Engl J Med* 2020; 382(9):845-54. doi: 10.1056/NEJMra1901593.
3. Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. *JAMA* 2014; 312(18):1905-17. doi: 10.1001/jama.2014.13259.
4. Guerra LO, Valdés FV. Molecular diagnostic of syphilis. *Enferm Infecc Microbiol Clin (Engl Ed)* 2020; 38 (Suppl 1):7-11. doi: 10.1016/j.eimc.2020.02.002.
5. Lum B, Sargent SR. Rapid Plasma Reagin. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK557732/>.
6. Motlagh MN, Javid CG. Presentation of ocular syphilis in a HIV-positive patient with false-negative serologic screening. *Case Rep Infect Dis* 2019; 2019:8191724. doi: 10.1155/2019/8191724.
7. Spydel LE. Congenital syphilis and the prozone phenomenon: a case study. *Adv Neonatal Care* 2018; 18(6):446-50. doi: 10.1097/anc.0000000000000573.
8. Chiu HY, Tsai TF. A crusted plaque on the right nipple. *JAMA* 2012; 308(4):403-4. doi: 10.1001/jama.2012.7538.
9. Ma DL, Vano-Galvan S. Images in clinical medicine. Syphilitic chancres of the lips. *N Engl J Med* 2013; 368(7):e8. doi: 10.1056/NEJMicm1202329.
10. Ficarra G, Carlos R. Syphilis: the renaissance of an old disease with oral implications. *Head Neck Pathol* 2009; 3(3):195-206. doi: 10.1007/s12105-009-0127-0.
11. Dourmishev LA, Dourmishev AL. Syphilis: uncommon presentations in adults. *Clin Dermatol* 2005; 23(6):555-64. doi: 10.1016/j.clindermatol.2005.01.015.
12. Otero-Rivas MM, Usero-Bárcena T, Rodríguez-Lojo R, et al. Multiple syphilitic chancre. *Med Clin (Barc)* 2018; 150(2):e3. doi: 10.1016/j.medcli.2017.03.011.
13. Katz AR, Johnson DW, Komeya AY, et al. Dermatologically challenging syphilis presentation. *Int J STD AIDS* 2019; 30(7):707-9. doi: 10.1177/0956462418817636.
14. Mainetti C, Scolari F, Lautenschlager S. The clinical spectrum of syphilitic balanitis of Follmann: report of five cases and a review of the literature. *J Eur Acad Dermatol Venereol* 2016; 30(10):1810-3. doi: 10.1111/jdv.13802.
15. Eccleston K, Collins L, Higgins SP. Primary syphilis. *Int J STD AIDS* 2008; 19(3):145-51. doi: 10.1258/ijsa.2007.007258.
16. Buffet M, Grange PA, Gerhardt P, et al. Diagnosing *treponema pallidum* in secondary syphilis by PCR and immunohistochemistry. *J Invest Dermatol* 2007; 127(10):2345-50. doi: 10.1038/sj.jid.5700888.
17. Hoang MP, High WA, Molberg KH. Secondary syphilis: a histologic and immunohistochemical evaluation. *J Cutan Pathol* 2004; 31(9):595-9. doi: 10.1111/j.0303-6987.2004.00236.x.
18. Engelkens HJ, ten Kate FJ, Judanarso J, et al. The localisation of treponemes and characterisation of the inflammatory infiltrate in skin biopsies from patients with primary or secondary syphilis, or early infectious yaws. *Genitourin Med* 1993; 69(2):102-7. doi: 10.1136/sti.69.2.102.

中文摘要

万能模仿者：梅毒硬下疳的非典型皮肤表现

巩慧子，吴梦茵，李军，郑和义

中国医学科学院 北京协和医学院，北京协和医院皮肤科

摘要

目的 本研究探讨了梅毒硬下疳误诊的原因，以期加强临床医师对此病不典型特征的认识。

方法 我们纳入了 27 例因临床表现不典型导致误诊和漏诊的梅毒硬下疳患者。

结果 女性患者的不典型表现主要为生殖器外的乳头红斑或糜烂性皮损，易被误诊为 Paget 病或湿疹。男性患者的不典型表现主要有多发性病变、梅毒龟头炎及非典型部位（如阴茎根部及邻近耻骨部位）的硬下疳。此外，非梅毒螺旋体试验阴性的患者也容易被漏诊或误诊。

结论 梅毒硬下疳的非典型表现多种多样，主要包括多发性病变、非典型部位、非梅毒螺旋体检测结果阴性，临床医师需警惕由此导致的漏诊或误诊。

关键词： 初期梅毒；梅毒硬下疳；误诊