Case Report

Syphilitic Meningitis in a Human Immunodeficiency Virus-Negative Woman

Saori Minato, MD[1] Takeshi Yamashita, MD, PhD[1] Katsuyuki Yoshida, MD[1] Ai Kawamura MD[1]
Tamami Watanabe, MD[1] Akira Ishii, MD[1] Takahiko Fukuchi, MD, PhD, MPH[1]
Hitoshi Sugawara, MD, PhD, FACP[1] Masaaki Kawase, MD, PhD[2] Toshio Demitsu, MD, PhD[2]

[1] Division of General Medicine, Department of Comprehensive Medicine 1, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama City, Saitama 330-8503, Japan.
[2] Division of Dermatology, Department of Comprehensive Medicine 2, Saitama Medical Center, Jichi Medical University, Saitama, Japan, 1-847 Amanuma-cho, Omiya-ku, Saitama City, Saitama 330-8503, Japan.

Abstract

The "Stop! Syphilis Project" was started in Japan in 2018.
A 29-year-old woman was admitted with fever, acute onset of posterior cervical pain, urodynia, and positive signs of meningeal irritation. Three months before admission, her heterosexual partner had been diagnosed with primary symptomatic syphilis with induration, but her initial serological screening tests for syphilis [rapid plasma reagin (RPR) test and *Treponema pallidum* hemagglutination (TPHA) test] were negative. She presented with a painless genital lesion at 2 months before the current hospitalization and with skin rashes at 1 month before hospitalization ; however, these were not recognized as symptomatic for syphilis. Additionally, urodynia appeared at 2 weeks before admission ; the patient underwent serological rescreening for syphilis, which tested positive (RPR : 128-fold, TPHA : 640.0 titer unit), and posterior cervical pain appeared at 10 days before hospitalization. After emergent hospitalization, she was diagnosed with syphilitic meningitis without human immunodeficiency virus infection. Antimicrobial treatment with penicillin G was continued for 2 weeks, after which the fever, posterior cervical pain, urodynia, and rash subsided, and the patient was discharged on hospital day 16. On day 187 after starting treatment, RPR was 8-fold and TPHA was 262.4 titer unit.
This case report highlights the fact that for the timely detection and appropriate treatment of syphilis, primary care physicians should recommend a repeated RPR test with incubation period taken into account, even in the absence of symptoms and even if initial screening results are negative.
(Key words : rapid plasma reagin (RPR) test, syphilis, syphilitic meningitis, *Treponema pallidum* hemagglutination (TPHA) test)

Introduction

Syphilis is a reemerging sexually transmitted disease caused by the spirochete *Treponema pallidum*. Syphilis remains a major public health problem not only in Japan but also in the world at large[1]. In Japan, notification of all detected cases of syphilis began in 1948 under the Venereal Disease Prevention Law[1]. Further, syphilis was classified as a category V notifiable infectious disease by the Infectious Diseases Control Law in April 1999, which was updated in 2007[1, 2], and all diagnosing physicians must notify the nearby health center within 7 days[1].

The number of reported syphilis cases has been rapidly rising since 2011[1]. Specifically, 5,820 cases were reported in 2017, which is approximately 9.4 times higher than the 621 cases reported in 2010[3]. There has also been a marked increase in syphilis among women, from 124 syphilis cases in 2010 to 1,895 cases in 2017[3]. Young women are at particular risk[2], as reports of congenital syphilis have

Correspondence to : Hitoshi Sugawara, MD, PhD, FACP Division of General Medicine, Department of Comprehensive Medicine 1, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama City, Saitama 330-8503, Japan.
Tel : +81-48-647-2111 Fax : +81-48-648-5188 E-mail : hsmdfacp@jichi.ac.jp Received : 3 September 2018, Accepted : 14 December 2018

increased recently[2] ; previously, this condition had almost disappeared[1]. The National Institute of Infectious Disease publicly acknowledged this increase in syphilis prevalence on November 13, 2015[4], and eventually, the "Stop! Syphilis Project" was started in May 2018[5].

However, the symptoms and signs of syphilis, which mimic that of many other diseases and vary during the 4 stages of disease, namely, primary, secondary, latent, and tertiary, have led to this infection being known as one of "the great imitators." It was Sir William Osler who said[6], "He who knows syphilis, knows medicine." It is difficult to clinically diagnose syphilis during its early stages, regardless of whether patients provide information on potential sources of contact.

This case report highlights the fact that for timely detection and appropriate treatment of syphilis, primary care physicians should recommend a rapid plasma reagin (RPR) test with incubation period taken into account, even if initial results are negative after the possible exposure.

Case

A 29-year-old woman presented to our department with fever, acute onset of posterior cervical pain, urodynia, and positive signs of meningeal irritation. Twelve weeks before this admission, her heterosexual partner had been diagnosed with primary syphilis, which was recognized due to the presence of penile induration. The patient reported having had sexual intercourse with this partner 14 weeks before admission. She immediately underwent initial serological screening for syphilis [RPR test, and *T. pallidum* hemagglutination (TPHA) test] ; however, the results were negative. Eight weeks before current admission, she had been prescribed gentamicin ointment for a 5×7mm painless ulcerative genital lesion by her general practitioner. Four weeks before current admission, pink-to-red macules had spread to her trunk and the entire abdominal region, and it did not improve despite antiallergic treatment. Two weeks before admission, urodynia developed and serological screening tests for syphilis were repeated. Posterior cervical pain that was unresponsive to loxoprofen developed 10 days before admission ; the results of the repeat serological tests for syphilis were reported as positive [RPR, 128-fold ; TPHA, 640.0 titer unit (T.U.)], and she was hospitalized for suspected meningitis. Patient history was otherwise unremarkable.

On examination, she was alert, temperature was 38.7°C, pulse rate was 95 beats per min and regular, blood pressure was 116/68 mmHg, respiratory rate was 18 breaths per min, and oxygen saturation was 98% on ambient air. Pink-to-red, discrete, maculopapular lesions 2–5 mm in size were noted on the trunk (Fig. 1A) and arms (Fig. 1B). A 9-mm diameter painful ulcer was observed on her labia minora (Fig. 1C). She showed signs of nuchal rigidity and jolt accentuation.

Laboratory tests were notable for white blood cells 7,300/μL (segments, 73.0% ; lymphocytes, 10.0% ; monocytes, 16.0% ; and eosinocytes, 1.0%) ; CRP 10.7 mg/dL ; RPR 128-fold ; TPHA 1,270 T.U. ; fluorescent treponemal antibody-absorption test (FTA-ABS) 320-fold ; and negative human immunodeficiency virus (HIV) antibody test. Cerebrospinal

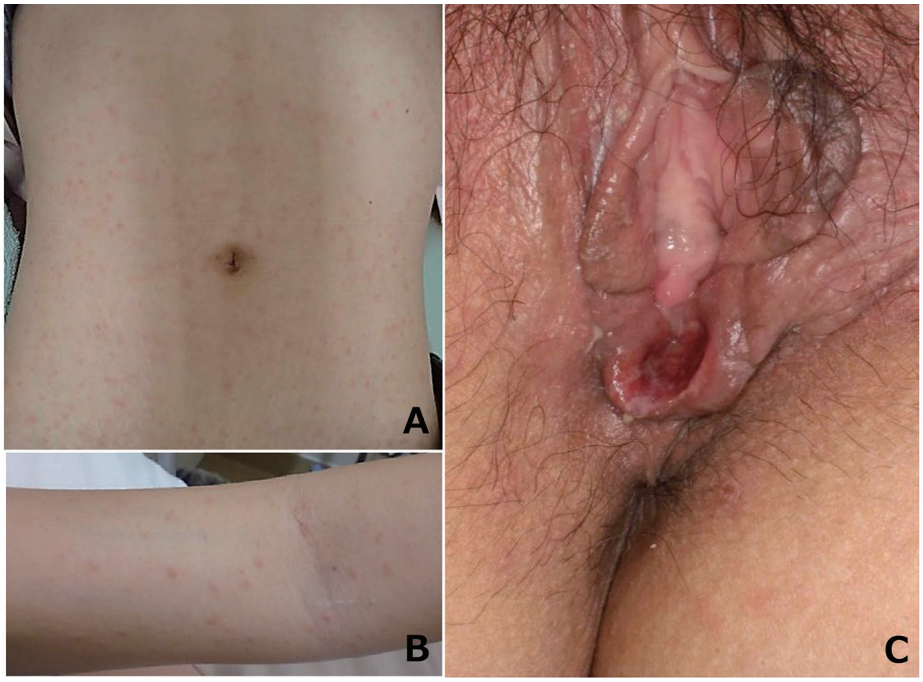

Figure 1. Skin lesions on admission. Pink-to-red discrete macular lesions 2 to 5 mm in diameter on the trunk (A), similar skin rashes on the arms (B), and a painful and deep small fingernail-sized ulcer on the labia minora (C).

fluid (CSF) assessment showed an initial CSF pressure of 315 mm CSF with a water-colored tone, total protein of 25 mg/dL, sugar of 51 mg/dL, cell count of 16/μL (mononuclear, 13; polynuclear, 3), and borderline (±) qualitative RPR. Head computed tomography (CT) showed no bleeding or space-occupying lesions. Ophthalmologic examination revealed no iritis, uveitis, or retinochoroiditis. A skin biopsy of the abdominal lesion revealed mild lymphocyte infiltration, and the results of uterine cervix or vaginal cytology were nonspecific. Tests for the herpes simplex virus antigens and Tzanck smear of the genital ulcer scrapings were not performed.

The clinical course of the patient is shown in Fig. 2. A working diagnosis of meningitis was established because of CSF findings and signs of meningeal irritation. Given the possibility of syphilitic meningitis, herpes simplex encephalitis, and genital ulcer, ceftriaxone (2 g, 2 times per day) and acyclovir (250 mg, 3 times per day) were started. A definitive diagnosis of syphilitic meningitis was made on day 5 and was based on positive serological tests for syphilis, cervical rigidity, positive jolt accentuation, high CSF pressure, borderline (±) CSF-RPR, CSF pleocytosis >5 cells/μL (13 cells/μL), and negative blood and CSF cultures, and on the CSF being negative for herpes simplex virus, tested using DNA-polymerase chain reaction[7]. From hospital day 5 onwards, antibacterial therapy was switched to 4 million units penicillin G, administered intravenously every four hours for 14 days[7–9]. She was discharged on hospital day 16, because the fever, posterior cervical pain, rash, and urodynia had subsided, and she was followed up one or two times a month on an outpatient basis until RPR was < 8-fold.[9] She performed normal daily activities on day 187 after treatment initiation, RPR was 8-fold and TPHA was 262.4 T.U.

Discussion

Our patient voluntarily reported to a medical clinic due to concerns about exposure after heterosexual contact with a partner who had been diagnosed with primary syphilis. Although she repeatedly visited the medical clinic despite

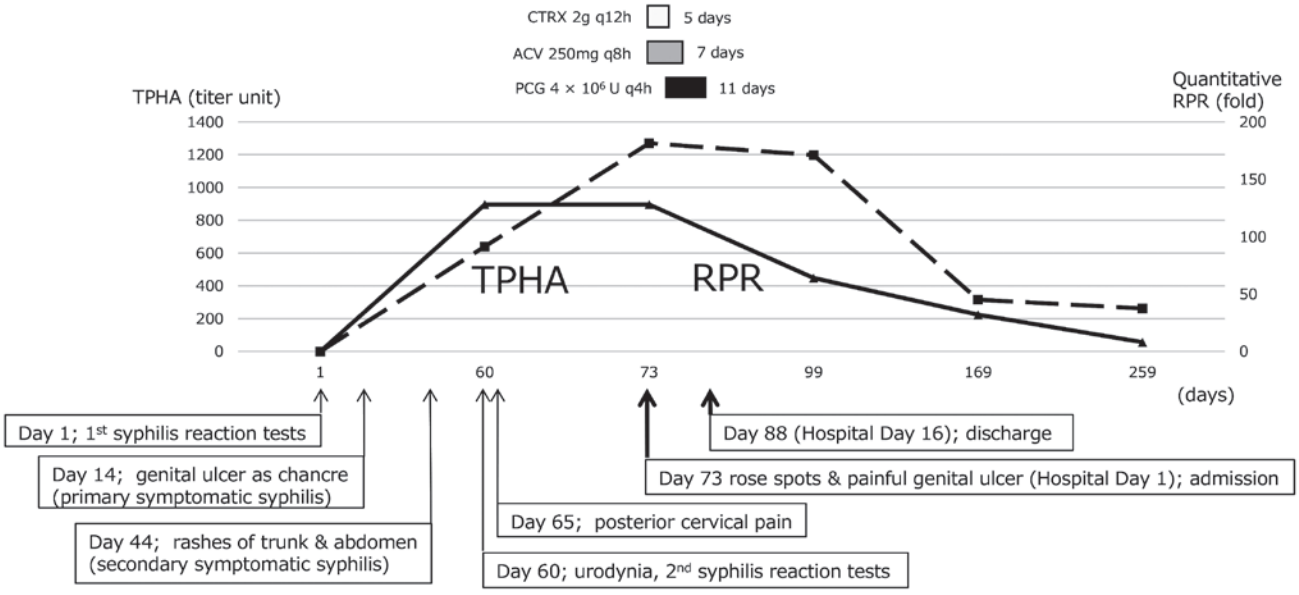

Figure 2. Clinical course showing RRR and TPHA titers, treatment regimens, and relevant clinical signs and symptoms. The day that the initial serum syphilis screening test results were reported negative and the patient had no subjective symptoms was designated day 1, because the first contact date for syphilis infection could not be identified in this patient. The genital ulcer developed on day 14, when the patient appeared to have had primary syphilis. Syphilitic roseola occurred on her trunk and abdominal region on day 44, indicating secondary syphilis. On day 60, serum syphilis tests became positive [RPR, 128-fold; TPHA, 640.0 titer unit (T.U.)]. On day 65, posterior cervical pain occurred, indicating syphilitic meningitis. Serum antibody titers of syphilis tests reached their peaks on admission on day 73 (RPR, 128-fold; TPHA, 1,270.0 T.U.); FTA-ABS, 320-fold) and decreased on day 259 (day 187 after starting treatment) to RPR 8-fold, TPHA 262.4 T.U., and FTA-ABS 80-fold. CTRX, ceftriaxone; ACV, acyclovir; PG, benzylpenicillin; RRR, rapid plasma reagin; TPHA, *T. pallidum* hemagglutination

initial negative results of serological screening for syphilis, her presenting symptoms were not recognized as indicating primary or secondary syphilis.

Three important clinical issues arise from the clinical course of this patient. First, what was the reason for the delay in establishing a definitive diagnosis of syphilis? Second, can a borderline (±) CSF-RPR result indicate the presence of syphilitic meningitis? And third, why does a genital ulcer (Figure 1C) persist until the phase of secondary syphilis?

Although the patient had reported her exposure to syphilis, her general practitioner did not recommend a repeated RPR test with incubation period taken into account after the initially negative RPR and TPHA tests. More importantly, these screening tests were not repeated, even after the genital chancre or the maculopapular rash had appeared. Thus, based on the clinical course described here, a repeated RPR test[9] should be recommended in cases of suspected syphilis exposure, even if initial RPR and TPHA results are negative and the patient has no symptoms or does not notice any rash or hard spots. Primary syphilis occurs following an incubation period of approximately 10–90 days after exposure to syphilis [10]. RPR does not yield reactive until approximately 4 weeks after syphilis infection[9] and its titers reflects disease activity ; therefore, the titers increase as disease progresses from incubation period to early syphilis. The positive rate of RPR in primary syphilis is approximately 80%. Therefore, even though RPR is negative immediately after exposure to syphilis or in the early stage of disease, RPR should be repeated when syphilis is suspected.

RPR is a non-treponemal test for syphilis that is widely used as a screening test. As disease specificity for CSF-RPR is high, a positive result can be used to diagnose neurosyphilis [11]. Even though the overall positive rate for CSF-RPR is low, at approximately 50% [11,12], a nonreactive CSF-RPR result cannot be used to exclude a diagnosis of neurosyphilis as CSF-RPR may remain nonreactive even when the CSF-Venereal Disease Research Laboratory (VDRL) test is reactive[7]. European guidelines prefer the results of the CSF-VDRL over those of the CSF-RPR[13]. However, the VDRL test is not available in some areas of the world, including in Japan[9], and unfortunately, there are no gold standard tests for diagnosing neurosyphilis[14]. Moreover, symptomatic meningitis as a complication of secondary syphilis is rare[8, 10, 14]. According to the algorithm established[7], regardless of the CSF-RPR result, in patients with suspected asymptomatic neurosyphilis and without HIV infection, either CSF pleocytosis >5 cells/ μ L or CSF protein concentration >45 mg/dL is consistent with neurosyphilis in the absence of other known causes ; however, CSF protein elevation may be less specific than CSF pleocytosis[7]. In the case described here, the combination of reactive serologic syphilis tests, borderline CSF-RPR, and CSF pleocytosis helped distinguish syphilitic meningitis from other infectious and noninfectious entities as part of the differential diagnosis[8].

The genital ulcer (Figure 1C), which was seen on admission, appeared atypical as a chancre, because it was deep, painful, and persisted until the secondary phase of syphilis. It is difficult to distinguish among the following differential diagnoses of atypical persistent chancre, namely, genital herpes, ulcerative syphilis tuberosa, or lues maligna[15]. The symptoms and signs of syphilis have led to the infection being known as "the great imposter or the great imitator" because of its wide-ranging clinical presentation[16]. The genital ulcer in our patient steadily subsided after the treatment with antibiotics and acyclovir. In conclusion, this case report highlights the need for primary care physicians to recommend a repeated RPR test with incubation period taken into account in patients with possible exposure to syphilis for earlier detection and appropriate treatment, even if the initial serological results are negative. In addition, proactive dissemination of knowledge among health care professionals on the prevention of sexually transmitted diseases (STDs) in the general population[5] and implementation of promotional activities for early detection and treatment STDs will be beneficial [1].

References

1. National Institute of Infectious Disease and Tuberculosis and Infectious Diseases Control Division Ministry of Health Labor and Welfare. <The Topic of This Month> Syphilis 2008-2014. IASR (Infectious Agents Surveillance Report) 2015 ; 36 : 17–18.
2. Takahashi T, Arima Y, Yamagishi T, et al. Rapid Increase in Reports of Syphilis Associated With Men Who Have Sex With Women and Women Who Have Sex With Men, Japan, 2012 to 2016. Sexually Transmitted Diseases 2018 ; 45 : 139–143.
3. Ministry of Health Labor and Welfare. Number of sexually transmitted diseases. http://www.mhlw.go.jp/topics/2005/04/tp0411-1.html (in Japanese) [Accessed June 16, 2018]
4. National Institute of Infectious Diseases. Infectious Diseases Weekly Report (IDWR). Increase in Syphilis notifications and characteristics of reported cases, as of October 2015. https://www.niid.go.jp/niid/en/survei/2292-idwr/idwr-article-en/6203-idwrc-1544-en.html [Accessed June 16, 2018].
5. Japanese Society for Sexually Transmitted Infections. Stop! Syphilis Project. http://jssti.umin.jp/prevention/syphilis.html (in Japanese) [Accessed June 16, 2018].
6. Lahav G, Lahav Y, Ciobotaro P, Ziv N, Halperin D. Laryngeal syphilis : a case report. Arch of Otolaryngol

Head Neck Surg 2011；137：294–297.
7. Marra CM. Neurosyphilis. Post TW, ed. UpToDate. Waltham, MA：UpToDate Inc. http://www.uptodate.com [Accessed on June 16, 2018].
8. Randolf JD, Tramont EC, Salazar JC. Syphilis（Treponema pallidum）. in：Mandell, Douglas and Bennet's Pronciples of Infectious Diseases 8th edn. Douglas, Mandell, Bennett, John E, Dolin, Raphael, Blaser, Martin J Eds. Philadelphia：Elsevier Saunders, 2015：2684–2709.
9. Japanese Society of Sexually Transmitted Infections. Syphilis（in Japanese）. Japanese Journal of Sexually Transmitted Infections 2016；27：48–52.
10. Golden MR, Marra CM, Holmes KK. Update on syphilis：resurgence of an old problem. JAMA 2003；290：1510-1514.
11. Marra CM, Tantalo LC, Maxwell CL, et al. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. Sex Transm Dis 2012；39：453–457.
12. Zhang H-L, Lin L-R, Liu G-L, et al. Clinical spectrum of neurosyphilis among HIV-negative patients in the modern era. Dermatology（Basel, Switzerland）2013；226：148–156.
13. Janier M, Hegyi V, Dupin N, et al. 2014 European guideline on the management of syphilis. JEADV 2014；28：1581–1593.
14. Ghanem KG. Neurosyphilis：A historical perspective and review. CNS Neurosci Ther 2010；16：e157–e168.
15. Watson KMT, White JML, Salisbury JR, et al. Lues maligna. Clin Exp Dermatol 2004；29：625–627.
16. Aman S, Hasleton P, Hanna A. The great imposter, the great imitator. Br J Cardiol 2011；118：94–96.

Funding sources

The study is not funded by a specific project grant.

Declaration of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Acknowledgment

This case report was presented at the 144th annual meeting of the Japanese Society of Internal Medicine in April 2017. The authors would like to thank Enago（www.enago.jp）for the English language review.

Jichi Medical University Journal 2018, 41, 29-34

梅毒性髄膜炎を発症したヒト免疫不全ウイルス非感染女性の1例

湊　さおり[1]，山下　武志[1]，吉田　克之[1]，川村　　愛[1]，渡辺　珠美[1]，石井　　彰[1]，福地　貴彦[1]，
菅原　　斉[1]，川瀬　正昭[2]，出光　俊郎[2]

[1] 自治医科大学附属さいたま医療センター　総合診療科　〒330-8503 埼玉県さいたま市大宮区天沼町１丁目847番地
[2] 自治医科大学附属さいたま医療センター　皮膚科　〒330-8503 埼玉県さいたま市大宮区天沼町１丁目847番地

要　　約

症例は，29歳女性。主訴は発熱，皮疹，急性発症の後頸部部痛および排尿時痛。入院３か月前にパートナーの第１期梅毒発症が判明。その翌日，近医にて，血清梅毒スクリーニング検査（rapid plasma reagin [RPR] test，Treponema pallidum hemagglutination [TPHA] test）を受けたが，いずれも陰性。２か月前，陰部皮疹に気づき，１か月前からの体幹部と腹部の点状紅斑の拡大もあったが，梅毒の診断には至らず。２週間前から排尿時痛あり。遂に２回目の梅毒スクリーニング検査を実施。入院10日前の後頚部痛出現時に，RPR 128倍とTPHA 640.0 titer unitとが判明し，緊急入院。髄液検査後，ヒト免疫不全ウイルス未感染の梅毒性髄膜炎と診断。Penicillin Gによる抗菌薬治療を２週間継続し改善。第16病日に退院し，治療開始第187日目には，RPR ８倍，TPHA 262.4 titer unitとなった。
梅毒を早期診断し適切に治療するには，梅毒曝露の可能性がある場合，１回目の梅毒スクリーニング検査が陰性でも，症状の有無にかかわらず，潜伏期を考慮して２回目以降の梅毒検査を実施するべきである。
（キーワード：rapid plasma reagin test [RPR]，梅毒，梅毒性髄膜炎，*Treponema pallidum* hemagglutination [TPHA]）

連絡先：菅原　斉，自治医科大学附属さいたま医療センター　総合診療科，〒330-8503　埼玉県さいたま市大宮区天沼町1丁目847番地.
Tel：048-647-2111　Fax：048-648-5188　E-mail：fsmdfacp@jichi.ac.jp
受付：2018年９月３日，受理：2018年12月14日