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Case Report

Concurrent coronavirus disease 2019 and primary syphilis in a young man: A rare case report

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ABSTRACT

Introduction: The global rise of syphilis infections and the ongoing coronavirus disease 2019 (COVID-19) pandemic are causes for concern. We herein report a rare case of concurrent primary syphilis and COVID-19. **Case report:** A 29-year-old man was admitted with a diagnosis of COVID-19. Although COVID-19 pneumonia appeared during ciclesonide and favipiravir treatment, his symptoms improved without developing severe hypoxemia. A small, red ulcer on the left-side of his glans penis was noted and left inguinal lymph node swellings were detected on computed tomography (CT). He reported that his last engagement in sexual intercourse had been 3 months previously, and that his partner had subsequently been diagnosed with syphilis. Although both serum *Treponema pallidum* (TP) antibody and rapid plasma reagin (RPR) quantitative tests were negative on the day of admission, we clinically diagnosed a suspected case of primary syphilis and started treatment with amoxicillin (1500 mg/day). We subsequently learned that the TP antibody and RPR quantitative tests had been positive 4 days before starting syphilis treatment. Amoxicillin treatment was continued for 61 days, and the ulcer gradually improved. One year later, the RPR quantitative test was negative, and CT revealed a reduction in size of the inguinal lymph nodes and no residual signs of COVID-19 pneumonia.

Conclusion: The prevalence of syphilis has been increasing even during the COVID-19 pandemic, and the incidence of concurrent syphilis and COVID-19 might be higher than is recognized. Asking patients with COVID-19 about high-risk sexual behavior and genital lesions could help with early diagnosis of syphilis.

1. Introduction

The incidence of syphilis, one of the most famous sexually transmitted infections (STIs), has recently been increasing worldwide [1], including in Japan [2,3]. In Hiroshima City, four new cases of syphilis (all males) were diagnosed in 2014, and the incidence of syphilis started to increase in 2015 [4]. Following a decrease in the number of new cases reported in 2019 (74 cases, 48 male and 26 female patients) and 2020 (71 cases, 50 male and 21 female patients), the number of new cases increased again in 2021 to a total of 105 cases (72 male and 33 female patients), which tied with 2018 (105 cases, 67 male and 38 female patients) as the year with the highest number of newly diagnosed syphilis cases in the past decade [4].

Since December 2019, coronavirus disease 2019 (COVID-19) has

become a global pandemic [5]. The COVID-19 crisis appears to have affected people's sexual behavior. Previous studies have focused on the change in the number of newly diagnosed syphilis cases during the first several months of the COVID-19 pandemic [6,7]. In Madrid, the number of newly diagnosed syphilis cases during the first 26 weeks of the year was 425 in 2019, and it decreased by 73.2% to 114 in 2020 [6]. In the Czech Republic, the number of confirmed cases of early syphilis decreased during the first 3 months of the national lockdown due to COVID-19, and it subsequently increased [7]. The decrease in the number of newly diagnosed syphilis cases in Hiroshima City in 2020 may have been due to mandatory and voluntary social distancing measures in general, taken to prevent the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and death from COVID-19. Conversely, the rebound in the number of newly diagnosed

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syphilis cases in 2021 might reflect a reduced fear of COVID-19.

Despite the increase in the reported number of new syphilis cases, we were unable to find any previous reports of concurrent COVID-19 and syphilis. We herein report a rare case of concurrent primary syphilis and COVID-19 in a young man.

2. Case report

COVID-19

In the second half of 2020, a 29-year-old man presented with a 1-week history of high fever (around 38.0 °C), headache, and joint pain. He was diagnosed with COVID-19 on the basis of a positive result in the polymerase chain reaction test for SARS-CoV-2, and he was admitted to our hospital 7 days after the onset of his fever. He was an ex-smoker with a Brinkman index of 120, and his only medical history of note was acute tonsillitis 7 years previously.

On admission, the patient had a clear level of consciousness. He had a body temperature of 37.1 °C, a blood pressure of 133/87 mmHg, a pulse rate of 96 beats/min with a regular rhythm, and a percutaneous arterial oxygen saturation (SpO₂) of 96%. His body mass index was 25.9 kg/m². His heart sounds were normal without any murmurs, and his respiratory sounds were normal. He had palpable, enlarged, non-tender left inguinal lymph nodes. There were no peripheral skin lesions or peripheral edema.

Computed tomography (CT) revealed mild pleural thickening in both lower lung fields, without signs of COVID-19 pneumonia, such as ground-glass opacities or infiltrative shadows (Fig. 1A). Laboratory tests revealed a decreased white blood cell count (2700 cells/μL; normal range: 3300–8600 cells/μL) with a normal neutrophil percentage (49.4%; normal range: 40.0%–70.0%), a low eosinophil percentage (0.4%; normal range: 1.0%–4.0%), and mildly elevated C-reactive protein (0.95 mg/dL; normal range: <0.14 mg/dL).

We prescribed 200 μg of inhaled ciclesonide: 2 inhalations, twice daily, and favipiravir, 1800 mg every 12 hours on the 1st day and 800 mg every 12 hours on the 2nd to 14th days. Both ciclesonide and favipiravir were used as study drugs to treat COVID-19 according to a

clinical research protocol [8,9].

On the 7th day of admission, a follow-up CT revealed a mixture of newly appeared ground-glass opacities and infiltrative shadows in both lower lung fields, suggestive of COVID-19 pneumonia with organizing changes (Fig. 1B) [10]. As the patient had no fever, cough, or decrease in SpO₂, we did not prescribe additional medication for the COVID-19 pneumonia.

At the 1-year follow-up visit, the ground-glass opacities and infiltrative shadows had improved and the mild pleural thickening in both lower lung fields existed without any change on CT images (Fig. 1C).

Primary syphilis

On the 2nd day of admission, the patient informed us that he had noticed a painless, non-itchy red ulcer, the size of an adzuki bean, on the left-side of his glans penis (Fig. 2A). He reported that his last engagement in sexual intercourse with his sexual partner had been 3 months previously and that she had been diagnosed with syphilis 2 months previously. It was unclear whether she had received treatment for syphilis. One month previously, despite being asymptomatic, he had performed a serum *Treponema pallidum* (TP) antibody test and a rapid plasma reagin (RPR) quantitative test because of anxiety regarding syphilis at another clinic, and both tests had been negative. The ulcer on his glans penis did not improve after application of white petrolatum ointment. Lymph node swelling was palpable in his left inguinal lesion without tenderness, and two left inguinal lymph node swellings were detected on CT images on the 7th day of admission (the largest lymph node: 21.0 × 13.0 mm) (Fig. 3A). From a medical interview and the characteristics of the skin lesion, we suspected that the ulcer on his glans penis was a syphilitic chancre, and that the left inguinal lymph node swellings were inguinal syphilitic lymphadenitis [11–13].

We measured TP antibody titer and RPR quantitative value using leftover serum from the day of admission. The TP antibody titer was measured in our hospital using a fully automated chemiluminescence immunoassay: TPAb Abbott (Abbott Japan Co., Ltd.) kit, measured with an Alinity i analyzer (Abbott Japan Co., Ltd., Tokyo, Japan). The TP antibody titer was 0.24 (sample relative light units/cut off: S/CO) and

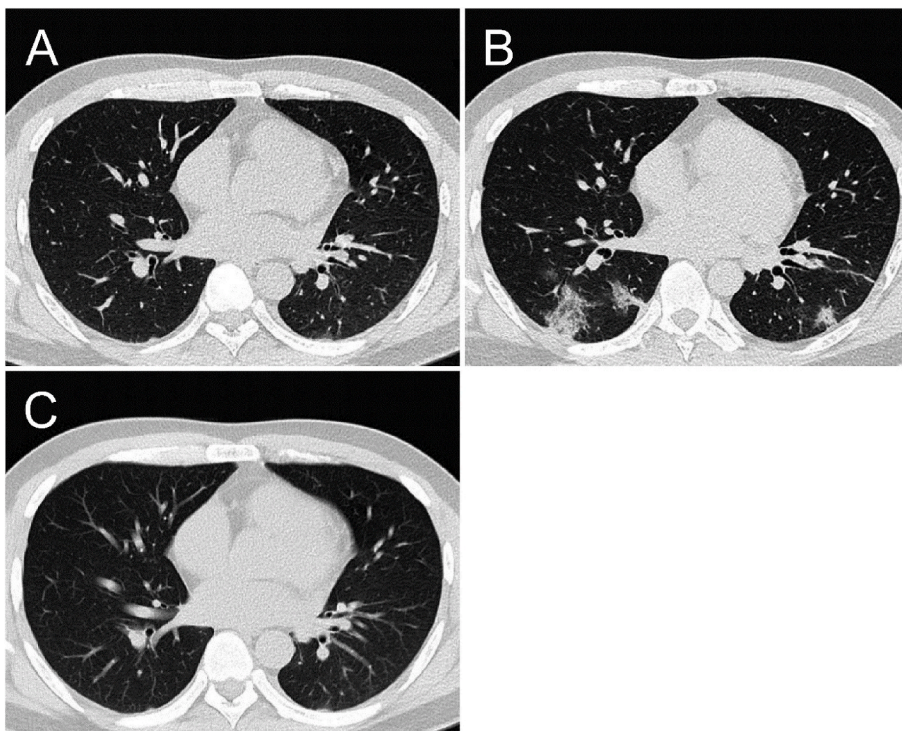


Fig. 1. Chest computed tomography (CT) images showing the clinical course of coronavirus disease 2019 (COVID-19) pneumonia.

A) CT image on the day of admission, showing mild pleural thickening in both lower lung fields. There are no ground-glass opacities or infiltrative shadows suggestive of COVID-19 pneumonia. B) CT image on the 7th day of admission, showing a mixture of newly appeared ground-glass opacities and infiltrative shadows in both lower lung fields suggestive of COVID-19 pneumonia with organizing changes. C) CT image taken 1 year later, showing a resolution of the ground-glass opacities and infiltrative shadows, and no change in the mild pleural thickening in both lower lung fields.

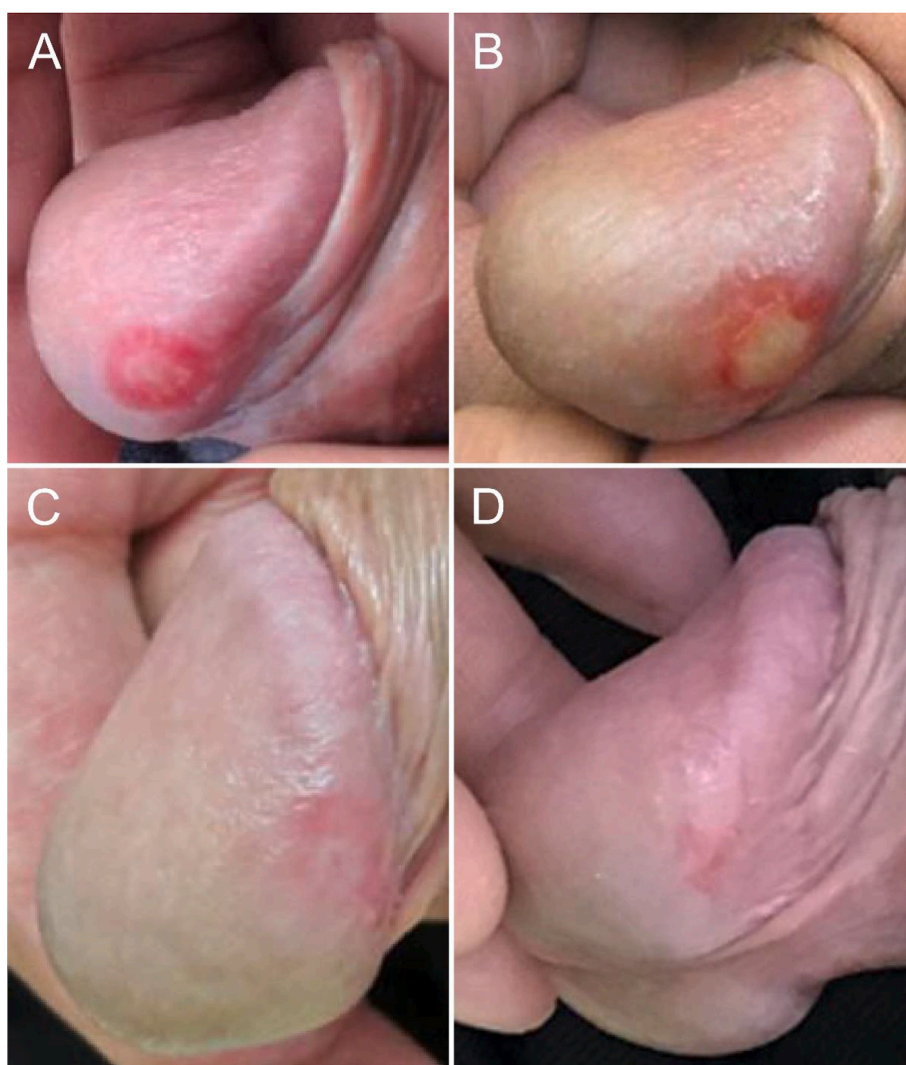


Fig. 2. Photographs showing the clinical course of the syphilitic chancre on the glans penis. A) A painless, non-itchy red ulcer, the size of an adzuki bean, on the left-side of the patient's glans penis. He informed us about this lesion on the 2nd day of admission. B) The ulcer on the 5th day of amoxicillin treatment, showing an increase in size. C) The ulcer on the 38th day of amoxicillin treatment, showing a decrease in size. D) Photograph of the glans penis taken 1 year later, showing no sign of the previous ulcer.

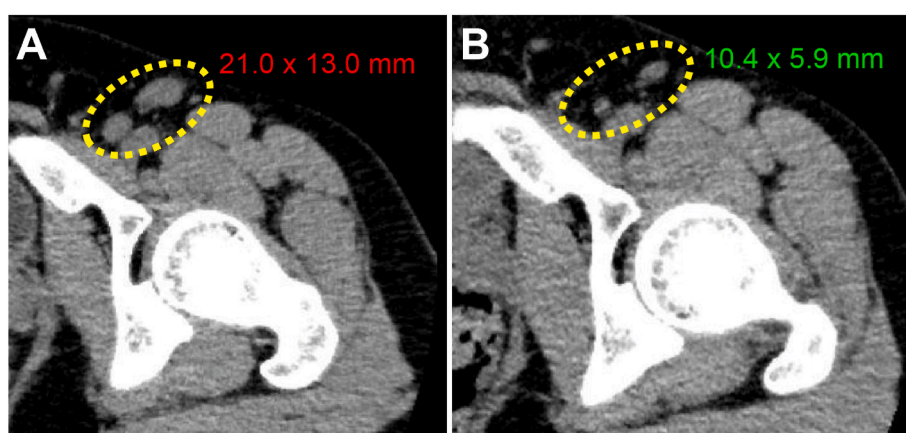


Fig. 3. Computed tomography (CT) images of two left inguinal lymph node swellings. A) CT image on the 7th day of admission, showing two swollen left inguinal lymph nodes (the largest lymph node: 21.0 × 13.0 mm). B) CT image taken 1 year later, showing a reduction in size of the two left inguinal lymph nodes (the largest lymph node: 10.4 × 5.9 mm).

reported as negative because it was lower than the positive cutoff value (≥ 1.0 S/CO) (Fig. 4). The RPR quantitative test was outsourced and measured by automated method using latex agglutination-turbidimetric immunoassay with a Mediace RPR (Sekisui Medical Co., Ltd., Tokyo,

Japan) measurement kit and a JCA-BM9010 (Jeol Ltd., Tokyo, Japan) analyzer. The value of RPR quantitative test was < 1.0 RPR units (RU) and reported as negative because it was lower than the positive cutoff value (≥ 1.0 RU) (Fig. 5).

Treponema pallidum antibody titer
(sample relative light units/cut off)

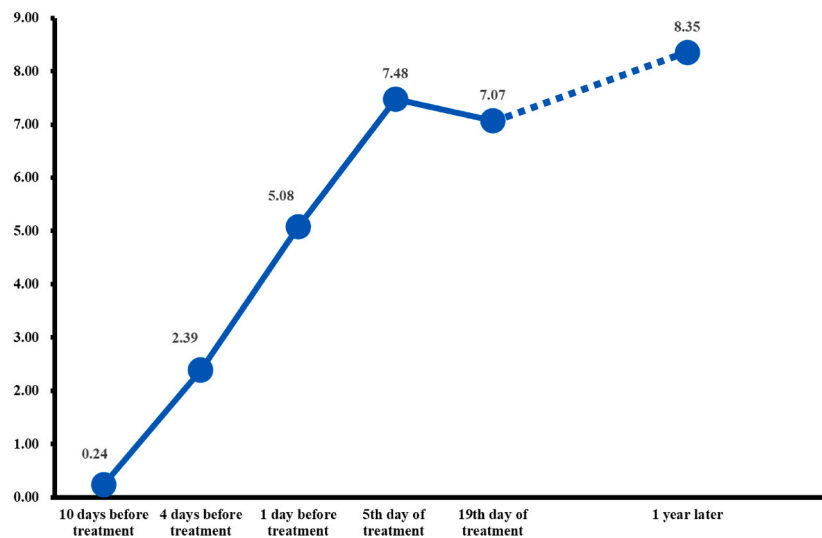


Fig. 4. Changes in the serum *Treponema pallidum* (TP) antibody titer over time. Although it was negative on the day of admission (10 days before starting syphilis treatment), it was positive on the 7th day of admission (4 days before starting syphilis treatment). The serum TP antibody titer continued increasing after starting amoxicillin treatment, and was the highest 1 year later.

Rapid plasma regain quantitative test result
(rapid plasma regain units)

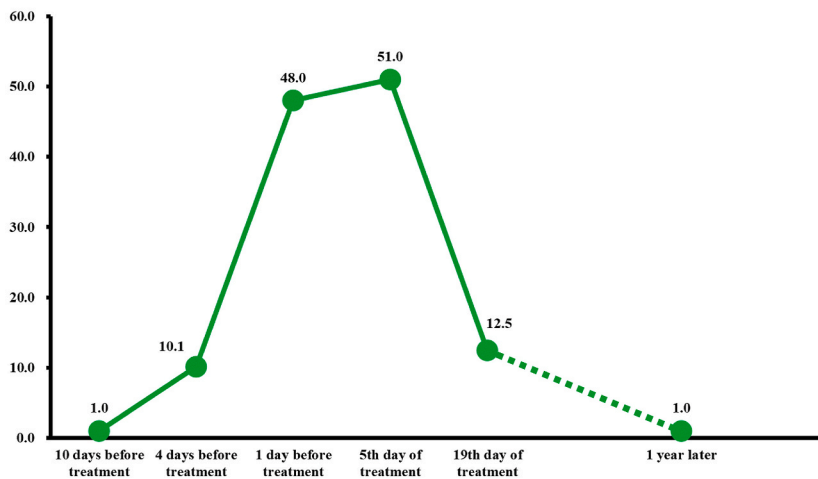


Fig. 5. Changes in the serum rapid plasma regain (RPR) quantitative test result over time. Although the RPR quantitative test result was negative on the day of admission (10 days before starting syphilis treatment), it was positive on the 7th day of admission (4 days before starting syphilis treatment). It peaked on the 5th day of amoxicillin treatment, and was lower on the 19th day of amoxicillin treatment. One year later, the RPR quantitative test result was negative and fulfilled the criteria for successful treatment: less than half the pretreatment value, measured using an automated method.

Despite these negative test results, we clinically diagnosed a suspected case of primary syphilis and started treatment with amoxicillin 1500 mg/day (divided into three doses) on the 11th day of admission. Approximately 14 hours after the amoxicillin was initiated, the patient’s body temperature increased to 37.9 °C, which we attributed to a Jarisch-Herxheimer reaction [14]. His fever improved with cooling with ice pack and did not recur. After starting syphilis treatment with amoxicillin, we retrospectively measured the serum TP antibody titer and the value of RPR quantitative test using leftover serum collected on the 7th day of admission (4 days before starting syphilis treatment). Based on the positive results of the two tests (serum TP antibody titer: 2.39 S/CO, Fig. 4 and RPR quantitative test: 10.1 RU, Fig. 5), we definitively diagnosed primary syphilis. An antibody test against human immunodeficiency virus-1,2 was negative.

The patient was discharged in a stable condition on the 13th day of admission (on the 3rd day of amoxicillin treatment). When the patient

was seen on the 5th day of amoxicillin treatment, the ulcer on his glans penis had become larger (Fig. 2B); however, it had become smaller by the 38th day of amoxicillin treatment (Fig. 2C). The patient continued taking amoxicillin for a total of 61 days. In addition, at the 1-year follow-up visit, the ulcer had disappeared (Fig. 2D), and the two left inguinal lymph nodes had decreased in size (the largest lymph node: 10.4 × 5.9 mm) on CT images (Fig. 3B). These findings confirmed our diagnosis of primary syphilis with a syphilitic chancre and left inguinal syphilitic lymphadenitis. The serum TP antibody titer continued increasing even after the treatment with amoxicillin, and it peaked 1 year later (Fig. 4). The RPR quantitative test value peaked on the 5th day of amoxicillin treatment and was decreased when measured on the 19th day of amoxicillin treatment. One year later, the RPR quantitative test result was negative and fulfilled the criteria for successful treatment: less than half the pretreatment value, measured using an automated method (Fig. 5).

3. Discussion

Syphilis is a major STI caused by *Treponema pallidum* subsp. *pallidum*. A syphilitic chancre appears as the typical lesion of primary syphilis 10–90 days after infection, following a latent period [11]. In Japan, the first choice of treatment for syphilis is oral penicillin, specifically, 1500 mg/day of amoxicillin for 4 weeks [12].

One of the most difficult aspects of clinical management of syphilis is achieving an early diagnosis of primary syphilis. Several patient and clinician factors lead to frequent overlooks of the diagnosis of primary syphilis. First, as suggested by the name, “the great imitator,” syphilis can cause a range of symptoms and lesions in various organs [15]. Clinicians, especially those who are not familiar with skin disease, should be careful not to miss the diagnosis of syphilis in patients with COVID-19 as complications thereof [16].

Second, patients may be unaware of the presence of a syphilitic chancre. Even if they are aware, they may fail to recognize the clinical significance of the lesion or may hesitate to tell medical staff about the lesion out of embarrassment. In the present case, the patient’s report of an ulcer on his glans penis and concern about possible syphilis was the only indication for performing the serum TP antibody and an RPR quantitative test.

Finally, most medical doctors have limited clinical experience of diagnosing syphilis and might misinterpret the results of serological tests. None of the internal medicine staff at our hospital had previously encountered syphilis in a patient, and the possibility of syphilis was almost excluded due to the initial negative result of the TP antibody and RPR quantitative tests on the day of admission, 3 months after the patient’s last reported engagement in sexual intercourse. Based on the expert advice of an experienced dermatologist, we repeated the two tests and confirmed our clinical diagnosis of primary syphilis.

Although the patient was infected with SARS-CoV-2 and admitted to the hospital with COVID-19, he was fortunate to have syphilis diagnosed during its primary phase and was able to start antibiotic treatment before reaching the latent phase, based on his suspicious background and lesion.

In patients with concurrent human immunodeficiency virus (HIV) infection and syphilis, there is a close relationship between the severity of impairment of the immune system induced by HIV infection and the response to syphilis treatment [17,18]. Knaute et al. [17] reported that patients with primary syphilis and HIV co-infection whose CD4⁺ T cell count was <500 cells/ μ L had a slower response to syphilis treatment than did patients with syphilis without HIV co-infection. Jinno et al. [18] found that in patients with syphilis and HIV co-infection, a CD4⁺ T cell count of <350 cells/ μ L was a significant risk factor for serological failure, defined as a lack of 4-fold decrease in value of the RPR quantitative test 9–12 months after treatment of early syphilis, including primary, secondary, and latent syphilis. These data suggest that impairment of the immune system, which manifests as a low CD4⁺ T cell count, can reduce the effectiveness of antibiotic treatment for syphilis.

Diao et al. [19] reported that patients with COVID-19 exhibit not only a reduction in CD4⁺ T cell, CD8⁺ T cell, and total T cell counts but also functional exhaustion of T cells. The reduction in the T cell count was larger with greater disease severity, and the T cell count was inversely correlated with serum levels of cytokines, including tumor necrosis factor- α , interleukin-6, and interleukin-10 released from monocytes and macrophages [19]. Based on these data, we consider that in the present case, there is a distinct possibility that the effectiveness of amoxicillin treatment was reduced and the healing of primary syphilis was delayed due to quantitative and qualitative T cell dysfunction induced by COVID-19.

In the present case, we believe that the interval from *Treponema pallidum* subsp. *pallidum* infection to the onset of the syphilitic chancre on the patient’s glans penis was not affected by concurrent COVID-19, because he had already noticed the ulcer on his glans penis before the onset of COVID-19 symptoms. However, we speculate that if he had

been infected with SARS-CoV-2 sooner after the onset of *T. pallidum* subsp. *pallidum* infection and had developed severe COVID-19 within the latent period of syphilis, his syphilitic chancre might have appeared much earlier with a shortened latent period because of the impairment of the immune system as described above. Little is known about the relationship and interaction between syphilis and COVID-19, and further studies are warranted to clarify the influence of COVID-19 on the clinical course of syphilis, and vice versa.

Previous studies have proposed several possible reasons for the increase in the number of the newly diagnosed cases of STIs, including changes in sexual behavior, commercial sex work, insufficient funding for prevention, poor education during school years, and an increase in the number of foreign visitors to Japan [2,3]. Suzuki et al. [20] reported that occurrence of syphilis was significantly associated with the rate of using dating applications. Dating applications could provide users with opportunities for sexual encounters with strangers even during the COVID-19 pandemic.

Considering that syphilis has been increasing in prevalence even during the COVID-19 epidemic, the concurrent incidence of these two diseases might be higher than is generally recognized. Thus, asking patients with COVID-19 whether they have any unusual lesions on their genitals could help with the early diagnosis of syphilis. Even if patients do not have suspicious lesions on their genitals, asking such questions could be useful for prompting patients to disclose high-risk sexual behaviors and risk factors for STIs and clinicians should perform TP antibody and RPR quantitative tests in suspected cases. Syphilis is often perceived to be an historical disease, and there is limited awareness that the prevalence of syphilis is currently increasing; therefore, continuing education of citizens regarding syphilis is important for preventing further spread.

Patient consent

The patient gave verbal informed consent for us to take pictures of the syphilitic chancre to use for publication. This is documented in his medical records.

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Authorship statement

All authors meet the ICMJE authorship criteria. All authors have contributed significantly to the work and approved submission of this manuscript. YK contributed with the drafting the manuscript to the final version with the help of RN, MO, KM, NI and TT. YK took part in the treatment of syphilis with expert advice from RN regarding treatment strategy, and evaluation of the treatment effect.

Declaration of competing interest

None.

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