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AUTHOR(S):

Shinohara, Koh; Furubayashi, Keiichi; Kojima, Yoko; Mori, Haruyo; Komano, Jun; Kawahata, Takuya

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Case Report

Clinical perspectives of *Treponema pallidum* subsp. *Endemicum* infection in adults, particularly men who have sex with men in the Kansai area, Japan: A case series

Koh Shinohara [a,b,*], Keiichi Furubayashi [c], Yoko Kojima [d], Haruyo Mori [d], Jun Komano [e], Takuya Kawahata [d]

[a] Department of Clinical Laboratory Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
[b] Department of Infectious Diseases, Kyoto City Hospital, Kyoto, Japan
[c] Sonezaki Furubayashi Clinic, Osaka, Japan
[d] Osaka Institute of Public Health, Osaka, Japan
[e] Osaka University of Pharmaceutical Sciences, Takatsuki, Japan

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ABSTRACT

Bejel, caused by *Treponema pallidum* subsp. *Endemicum* (TEN), is a locally transmitted disease among children and juveniles in hot and dry regions. The number of adult cases of TEN infection outside of endemic areas has recently increased. We clinically examined five cases of TEN infection among adult cases previously reported in Japan. TEN infection mainly developed among young to middle-aged men who have sex with men (MSM). The clinical features of cases of TEN infection were similar to those of primary- and secondary-stage *T. pallidum* subsp. *pallidum* (TPA) infection. Genital lesions were common as the primary lesion. The clinical features and laboratory parameters of cases of TEN infection were similar to those of TPA infection. Most of the isolated strains had the A2058G mutation in 23S rDNA, which is responsible for resistance to macrolides. We also performed the systemic literature review of the TEN cases outside the endemic countries. The recent reported cases diagnosed with molecular methods shared the clinical features, occurred in young-to middle-aged sexually active persons in urban areas of developed countries and often accompanied with genital lesions, which were distinct from the classic description of bejel. This case series and the literature review provides important clinical insights and will contribute to the clinical detection of this rarely identified disease in developed countries. The surveillance of treponematoses, including TEN infection, using molecular diagnostic techniques is also warranted in developed countries, for the purpose of grasping the epidemic situation and control the local transmission.

1. Introduction

All human treponematoses, including venereal syphilis, bejel (endemic syphilis), pinta, and yaws, share similar clinical features that are consistent with the genetic and antigenic relatedness of their etiological agents [1,2]. Bejel, also known as “non-venereal treponematoses”, is caused by *Treponema pallidum* subsp. *Endemicum* (TEN) [1]. Classically, bejel primarily affects children younger than 15 years of age in dry hot areas, such as the Middle East [1,2]. The mode of transmission of TEN is generally considered to be non-venereal, such as mucosal and skin contact with eating utensils or drinking vessels [1,2]. However, recent studies from France and Cuba that examined cases of TEN infection among sexually-active male, especially among men who have sex with men (MSM), suggested its transmission through sexual contact [3–5]. We previously reported 5 cases of TEN infection among MSM in Japan [6]. The findings obtained indicated the inclusion of TEN infection in *T. pallidum* subsp. *pallidum* (TPA) infections, such as venereal syphilis, in developed countries, which were historically considered to be bejel-free regions. Therefore, the clinical features of adult cases of TEN infection outside of endemic areas need to be elucidated in more detail. However, previous research focused on the epidemiological and genetic aspects of the pathogen, and, thus, limited information is

* Corresponding author. Department of Clinical Laboratory Medicine, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan.
E-mail addresses: shinoharakoh@kuhp.kyoto-u.ac.jp, shinoharakoh@kuhp.kyoto-u.ac.jp (K. Shinohara).

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currently available on the clinical features of TEN infection in developed countries. We herein report the clinical features of previously reported cases of bejel [6], and also conducted a literature review on molecularly diagnosed cases of TEN infection outside of endemic areas.

2. Case reports

2.1. Cases 1 and 2

Cases 1 and **2** were both males in their 20s, MSM, and had sexual intercourse 6 months prior to presentation. They developed penile ulcers or erosion (Fig. 1a), but did not exhibit systemic symptoms. They both had negative serum rapid plasma reagin (RPR) and *Treponema pallidum* latex agglutination (TPLA) tests, with values < 1.0 (RPR units (R.U.)) and <10.0 (titer units for anti-treponema antibodies (T.U.)), respectively. Swab samples were collected from penile lesions. Both patients were clinically diagnosed with primary syphilis and orally administered amoxicillin for 3 and 2 weeks, respectively. Following the completion of treatment, penile lesions had diminished in both cases.

2.2. Case 3

A male in his 40s presented with progressive bilateral neck swelling over 6 weeks. The patient was MSM, had sexual intercourse within 6 months before presentation, and had never traveled outside of Japan. Enlarged tonsils (Fig. 2a), bilateral cervical lymphadenopathy without tenderness, and a diffuse maculopapular rash were detected in a physical examination. Magnetic resonance imaging revealed lymphadenopathy in Waldeyer's ring and the cervical lymph nodes (Fig. 2b). Positron emission tomography/computed tomography (PET-CT) showed intense signals from Waldeyer's ring and the cervical lymph nodes (Fig. 2c). Since malignant lymphoma was suspected, cervical lymph node biopsy was performed. In the pre-operation examination, the RPR and TPLA tests were reactive. Specimens taken from the biopsied lymph node and a pharyngeal swab were subjected to molecular diagnostic analyses. *T. pallidum* was detected in both specimens via a polymerase chain reaction targeting *TpN47* and *polA*. Malignancy was pathologically discounted. Therefore, the patient was diagnosed with secondary syphilis and the oral administration of amoxicillin was initiated. Ten days later, amoxicillin was stopped because of skin eruptions and replaced with doxycycline for 2 weeks. Enlargement of the bilateral tonsils and cervical lymph nodes improved within 2 months. Temporal changes in serological RPR and TPLA test results before and after the treatment are shown in Table 1.

2.3. Case 4

A male in his 30s presented with multiple granulomas on the nose, genital and perianal regions, non-itchy eruptions on the bilateral palms, a penile ulcer and small nodules, and a reddish small nodule on the mons pubis (Fig. 1c–e). The patient was MSM who had sexual intercourse within 6 months before presentation. Serum RPR and TPLA values were 39.1 (R.U.) and 20,768 (T.U.), respectively. A specimen swabbed from the penile ulcer was subjected to molecular diagnostic analyses. The patient was diagnosed as secondary syphilis, and administered amoxicillin orally for 4 weeks. Following the completion of treatment, skin lesions had diminished in this case.

2.4. Case 5

Case 5 was a HIV-infected male being treated with anti-retroviral therapy who was MSM and had sexual intercourse within 6 months prior to presentation. The patient developed a penile ulcer (Fig. 1b). Serum RPR and TPLA values were <1.0 (R.U.) and 35.7 (T.U.), respectively. A specimen swabbed from the penile ulcer was subjected to molecular diagnostic analyses. The patient was diagnosed with primary syphilis, and oral administration of amoxicillin for one week was initiated. Following the completion of treatment, the penile ulcer had diminished in this case.

Summary of cases (Table 2).

The clinical features of the five cases with TEN infection were summarized in Table 2. All cases were diagnosed as TEN infection using

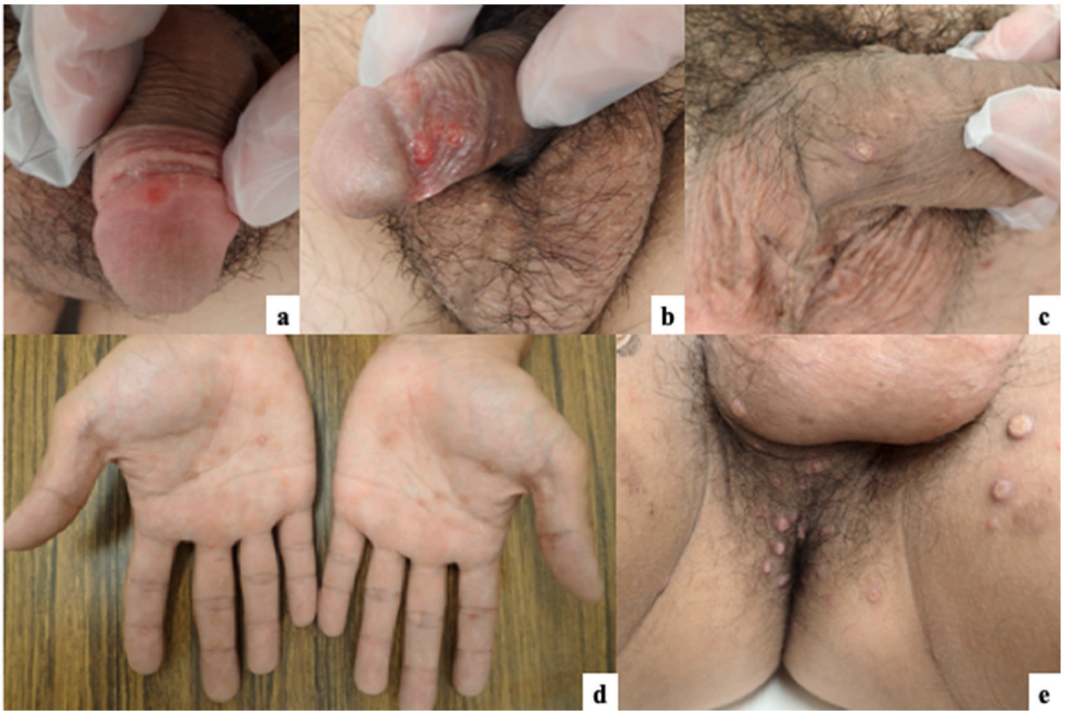

Fig. 1. Penile erosion in Case **2** (a) and Case 5 (b). Small nodules on the penis (c), non-itchy eruptions on both palms (d), and multiple granulomas on the genital and perianal regions (e) were observed in Case **4**.

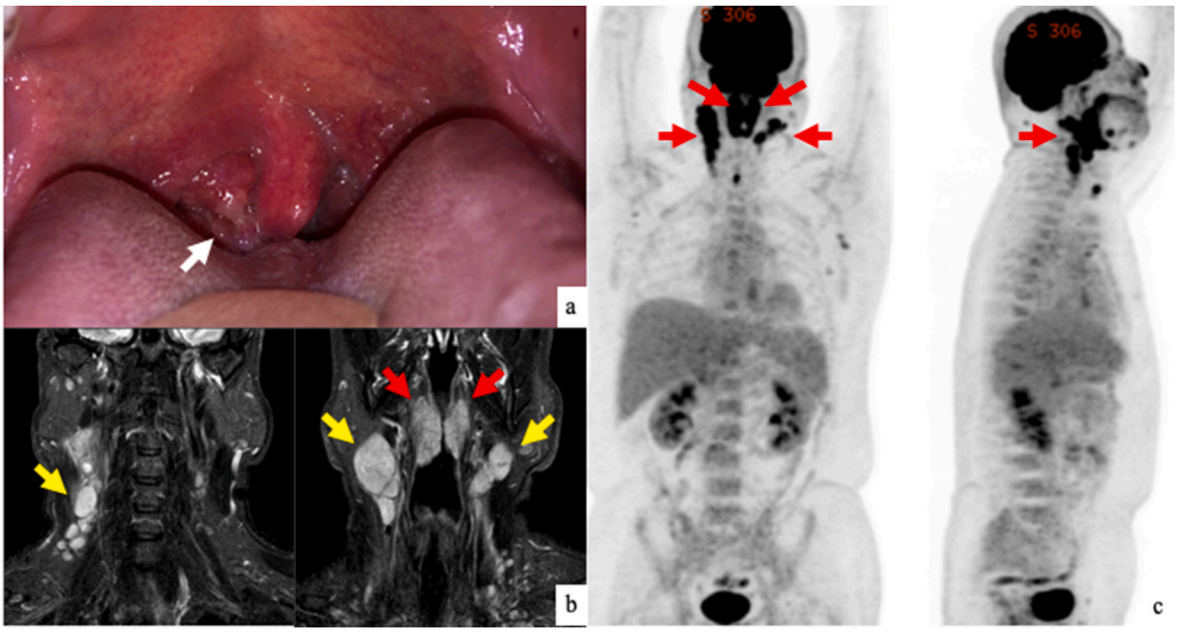

Fig. 2. (Case 3): (a) A pharyngeal examination revealed bilaterally enlarged tonsils with a thin white mucous film on the right tonsil (arrow). (b) Magnetic resonance (MR) imaging of the neck at presentation showing bilaterally enlarged tonsils (red arrow) and bilateral cervical lymphadenopathy, particularly on the right side (yellow arrow). (c) Positron emission tomography/computed tomography (PET/CT) showing a high intensity signal on Waldeyer's ring and the cervical lymph nodes (red arrow).

Table 1
Temporal changes in RPR and TPLA titers before and after antibiotic therapy in Case 3.

	Before treatment	1 month after treatment	4 months after treatment	6 months after treatment	12 months after treatment	18 months after treatment	24 months after treatment
TPLA titer (T.U.)	2370.0	1214.9	457.2	212.0	101.7	61.7	47.7
RPR titer (R.U.)	150.0	27.8	3.1	<1.0	<1.0	<1.0	<1.0

Abbreviations; RPR: rapid plasma reagin, R.U.: RPR units, based on the WHO standard. One R.U. is equal to 0.4 IU and is equivalent to the value using the RPR card method. A positive result is > 1 R U. TPLA: *Treponema pallidum* latex agglutination, T.U.: titer units for anti-treponema antibodies. One T.U. equals 2 mIU with WHO reference material. A positive result is > 10 T U.

molecular methods, as we previously reported [6,7]. In brief, we confirmed *Treponema pallidum* infection by using nucleic acid amplification tests targeting the TpN47 and *pol*A gene regions, which is specific for treponemal DNA, and TEN infection was confirmed based on the multi-locus sequence analysis of the tp0548 and tp0856 gene regions [6,7]. All cases were sexually active MSM living in the Kansai area in the western part of Japan, including Kyoto and Osaka. All patients denied the recent oversea travel; however, thorough history of foreign travel was not available other than Case 3, who had never traveled abroad. Early syphilis was initially suspected in all cases; 3 primary and 2 secondary stages. Four cases manifested genital lesions, and TEN infection was identified in samples collected from these lesions. Among cases in the secondary stage, non-itchy skin eruptions resembling rose spots, typically observed in TPA infection, or small nodules were noted in the genital and perianal regions (Fig. 1 c-e). No case was clinically suspected of having central nervous system involvement, bone lesions, or destructive osteitis. In serological treponema examinations, RPR and TPLA were non-reactive or weakly reactive in cases in the primary stage, whereas both were highly reactive in the two cases in the secondary stage. All cases were initially treated with oral amoxicillin. Although the doses and durations of treatment varied, clinical and serological improvements were observed in all cases. All patients harbored TEN infection with the A2058G mutation on the 23S rRNA gene, which conferred resistance to macrolides.

2.5. Systematic review of the literature

A literature review was performed on October 4, 2021, using the Pubmed and Web of Science databases, using the terms "bejel" OR "endemic syphilis" OR "*Treponema pallidum* subsp. *Endemicum*". We included articles from the English literature which described the cases of bejel outside the endemic countries, from Jan 1, 1970 to the end of September 2021. The period of the literature review was determined based on the fact that the WHO eradication campaign of endemic treponematoses was conducted in 1950s and 1960s and the global prevalence of endemic treponematoses had been dramatically reduced by early 1970s [1,2]. The endemic area of bejel was based on the WHO report [1,2]. We retrieved 131 articles from the Pubmed database, and 184 articles from the Web of Science database. Non-English papers, non-human study, non-case reports were excluded. Case reports that mentioned of non-TEN patients, and those reported from the endemic countries were also excluded. Finally, we reviewed 6 articles including 21 cases of TEN infection diagnosed outside the endemic area: Turkey, Canada, Iran, France, Cuba, and Japan [4–6,8–10] (Fig. 3). Of the cases, 13 cases were children under 20 years old, and 8 cases were adults. In the earlier study, the diagnosis was often made on the clinical features. Report from Turkey in 1995 included three siblings and their father [8]. The diagnosis was based on clinical features, especially on the facts that father had no genital lesion, mother was serologically negative, and two of the children suffered from bone and joint lesions but not complicated

Table 2
Clinical features of 5 cases of TEN infection.

CaseNo.	Age/ Sex	Year of consultation	Health care facility	Foreign travel history	HIV serostatus	Suspected area of acquisition	Presenting clinical symptoms	Initial diagnosis at presentation	Initial RPR titer (R. U.)	Initial TPLA titer (T. U.)	Site of TEN identified	Treatment	Outcome	A2058G mutation
1	20 M	2014	SFC	NA	negative	Osaka	penile ulcer	Primary syphilis	<1.0	<10.0	Exudate from the penile ulcer (Swab)	Amoxicillin 1500 mg/day for 3 weeks	successfully improved	(+)
2	24 M	2017	SFC	NA	negative	NA	penile erosion	Primary syphilis	<1.0	<10.0	Exudate from the penile erosion (Swab)	Amoxicillin 1500 mg/day for 2 weeks	successfully improved	(+)
3	47 M	2017	KCH	Never	negative	Osaka	bilateral tonsillitis, bilateral cervical lymphadenopathy, diffuse maculopapular rash	Secondary syphilis	150	2370	pharyngeal swab, cervical lymph nodes	Amoxicillin 3000 mg/day + probenecid 750 mg/day for 2 weeks, then doxycycline for 2 weeks	successfully improved	(+)
4	30 M	2017	SFC	NA	negative	Osaka	Multiple granulomas on the nose, genital and perianal regions, non-itchy eruptions on bilateral palms, a penile ulcer and small nodules, reddish small nodule on the mons pubis	Secondary syphilis	39.1	20768	Exudate from the penile ulcer (Swab)	Amoxicillin 1500 mg/day for 4 weeks	successfully improved	(+)
5	37 M	2018	SFC	NA	positive	NA	penile ulcer	Primary syphilis	<1.0	35.7	Exudate from the penile ulcer (Swab)	Amoxicillin 1500 mg/day for a week	successfully improved	(+)

Abbreviations; SFC: Sonezaki Furubayashi Clinic, KCH: Kyoto City Hospital, RPR: rapid plasma reagin, R.U.: RPR units, TPLA: *Treponema pallidum* latex agglutination, T.U.: titer units for anti-treponema antibodies, TEN: *Treponema pallidum* subsp. *Endemicum*, M: male, NA: not available.

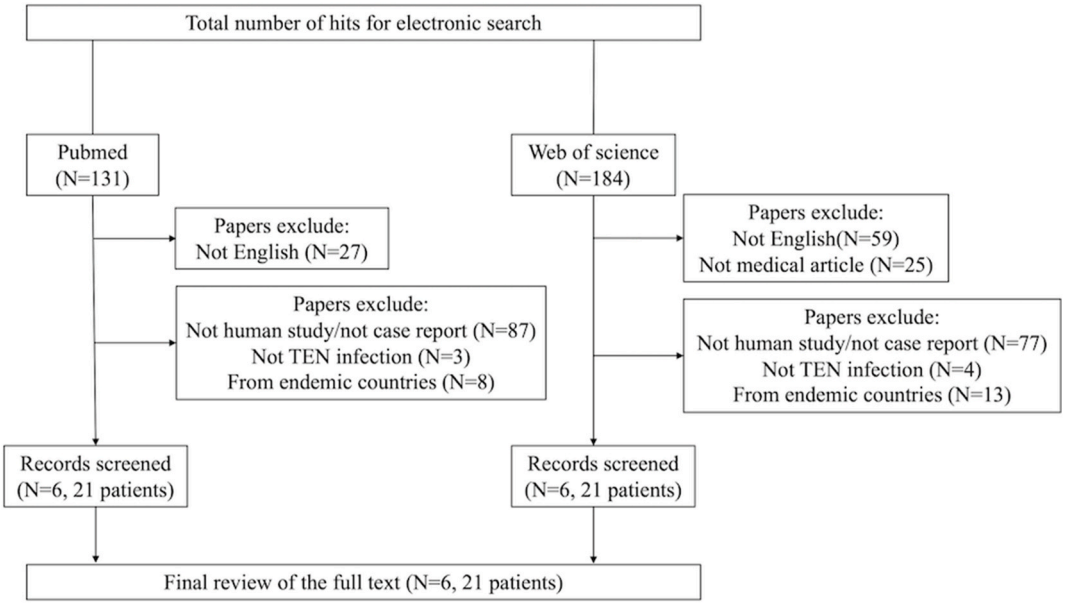

Fig. 3. Flow chart for the protocol employed for systemic review in this study.

with cardiovascular and neurological involvement [8]. In the Canada cases, the household, non-venereal transmission among nine children (one case was diagnosed with the detection of TEN by nuclear acid amplification test, and the other cases were diagnosed with serology) after the acquisition of TEN during the stay in Senegal were suspected, and the parents of children were negative for serology [9]. Seven of the nine cases were without any symptoms, but the other two cases had clinical lesions. One had skin papules, perianal condylomata and another had oral ulcer, hoarse voice, drooling, adenopathy [9]. The Iran case was a sporadic case in the remote rural distinct of low socioeconomic status, and he was 14-year boy without any sexual history, so non-venereal transmission among the local residents was suspected [10]. He had cutaneous lesions on his face and history of a rash without mucous membrane, and the diagnosis was based on clinical features [10]. In contrast, the recent reported studies, twelve sexually active adult patients, including our five cases, were diagnosed with TEN infection using molecular diagnostic methods (Table 3) [3–5]. All patients were male, and 10 (83%) were MSM. Most cases were in their 20s–40s. Five cases (42%) also had HIV. Genital lesions were observed in 10 cases (83%).

3. Discussion

We herein described the clinical features of 5 adult cases of TEN infection in Japan. And we have performed the systemic review of the literature of the cases with TEN infection outside the endemic countries. We found that 21 cases were reported as TEN infection diagnosed outside the endemic area. In the earlier reports, the cases of TEN infection shared the classic characteristic features of bejel, which mostly occurs in children, primarily affects skin and mucous membranes other than the genital area, was transmitted non-venereal route, and suspectedly infected in the rural area in the dry hot areas [1,2]. In contrast, the recent reported cases, using the molecular methods for diagnosis, hade several characteristic features, which were distinct from those of typical bejel cases. Most of the cases were sexually active young to middle-aged male, who lived in the urban areas with high socioeconomic status. Genital lesions were commonly observed in these patients with TEN infection and were macroscopically indistinguishable from those associated with TPA infection. These background and clinical features of the cases were similar to the typical features of TPA infection, venereal syphilis. Human treponematoses other than TPA infection have classically been recognized as non-venereal because they mainly affect children and rarely present with genital lesions [1,2]. Historically, the primary lesions of bejel were frequently not observed because of their small size and location within the oral and nasopharyngeal mucosa [1, 11]. Furthermore, the lack of genital lesions was previously considered to be crucial for differentiating bejel from venereal syphilis [12]. In early studies on bejel, venereal syphilis and bejel were distinguished solely based on epidemiological and clinical features [13]. In other words, human treponematoses were diagnosed as bejel in children in rural communities and as venereal syphilis in adults having sexual contacts. However, our case reports and the literature review showed that the reported clinical features of TEN infections outside the endemic countries were changed after the initiation of the molecular diagnostic

Table 3
Summary of a review of clinical features of cases of TEN infection among adults using molecular diagnostic methods.

Reference	Residency	Age in years, Median (IQR)	Male Sex	MSM	HIV-positive serostatus	Existence of genital lesions	Initial diagnosis at presentation	A2058G/A2059G mutation
3, 4	France	42	1/1 (100%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	Primary-stage syphilis: 1/1 (100%)	–
5	Cuba (Havana)	31 (22–47)	6/6 (100%)	4/6 (67%)	4/6 (67%)	5/6 (83%)	Not described	0/6
This study	Japan (Kansai area)	30 (24–37)	5/5 (100%)	5/5 (100%)	1/5 (20%)	4/5 (80%)	Primary-stage syphilis: 3/5 Secondary-stage syphilis: 2/5	5/5

Abbreviations; IQR: Interquartile range, MSM: men who have sex with men, HIV: human immunodeficiency virus.

methods, which indicates that the classical way of differentiation between TPA infection and TEN infection by clinical and epidemiological characteristics may not be sufficient. Our case reports and the literature review also indicated that TEN infection appears to be transmitted through sexual contact.

Considering that the clinical characteristics of TEN infection are very similar to those with TPA infection, and TEN were locally transmitted among the sexually active adults in Japan, there is a concern that TEN infection may spread a wide range of age groups. As previously mentioned, the mode of TEN transmission is considered to be non-venereal, such as mucosal and skin contact with eating utensils or drinking vessels [1,2]. This non-venereal mode of transmission may lead to the expansion of the infection other than sexually active adults, especially to children or elderlies. In case the TEN infection expands to these population, diagnosis of the cases is confounded by a lack of experienced clinicians and delayed diagnosis and treatment are concerned. Accurate diagnosis of the TEN infection and grasping the whole picture of the epidemic situation using the molecular diagnosis will control the local transmission of TEN, and prevent the expansion to a wide range of population.

Systemic symptoms corresponding to those of secondary-stage syphilis infection, such as systemic lymphadenopathy and generalized rash, may develop with TEN infection, and include clinical manifestations resembling malignant lymphoma, as observed in case 2. Early studies on bejel reported that a generalized rash, including macular roseola, and general adenopathy may develop [12–14]; however, few cases of endemic treponematoses exhibited image findings that resembled malignant lymphoma, such as excessive lymphadenopathy. This may be related to the poor access to image studies in the endemic countries of bejel. Our case series revealed that TEN infection may develop a broader range of symptoms than those described to date. In addition, our cases showed that the results of the RPR and TPHA tests corresponded to those with TPA infections. Both tests were highly reactive in secondary stage and tested negative or weakly reactive in primary stage. As previous reviews described the RPR and TPHA tests become reactive during all treponemal infections [1,2], the serologic tests are useful for treponemal infections, but they are not species-specific and not useful for differentiating the TEN infection from the TPA infection.

Another important finding was the presence of the A2058G mutation in 23S rDNA, which, to the best of our knowledge, was reported for the first time in cases of TEN [7]. A2058G and A2059G mutations in 23S rDNA have been linked to resistance to macrolides [15,16]. Geographical variations have been reported in the prevalence of these mutations in TPA [17]. These findings revealed a high prevalence of macrolide-resistant mutations in developed countries, such as the U.S., U.K., Australia, and Japan, and a relatively low prevalence in developing countries [7,17]. However, limited information is currently available on other treponemas. In a recent study, *T. pallidum* subsp. *pertenue*, a treponema causing yaws, contained the A2059G mutation [18]. Since macrolides including azithromycin are used to eliminate endemic human treponematoses in developing countries, the prevalence of these mutations is a major concern not only for clinical management, but also from a public health standpoint. In contrast to our findings, six strains from Cuba were also examined for A2058G and A2059G mutations in 23S rDNA, but none tested positive for these mutations. This finding suggests that the macrolide-resistant TEN strain is locally transmitted in Japan. This suggestion is supported by the finding that the sequence of tp0548-tp0856 genes is identical in all five strains, and distinct from the previously reported TEN strains, 11q/j, BosniaA and Iraq B [7]. This may represent that the local transmission of TEN in Japan could have been spread from one source, however, the resolution of the multi-locus sequence analysis using tp0548-tp0856 gene regions, with around 1200bp in length, would not be enough for demonstrating it. More comprehensive genetic analysis is warranted to investigate the detailed genetic features of local transmission.

There are a number of limitations that need to be addressed. Due to the small number of cases of TEN infection reported to date, the present case series may not accurately reflect the actual clinical features of TEN infection outside of endemic areas. Furthermore, since lumber puncture was not performed, CNS infection cannot be ruled out. Further studies are required to establish whether endemic treponematoses involve CNS infection and neurological sequelae [1]. Therefore, molecular surveillance and the accumulation of clinical information on molecularly identified cases of TEN infection are needed.

In conclusion, through a case series and the literature review of the cases outside the endemic areas, we herein showed indistinguishable clinical features between TEN and TPA infections among sexually active adults, and also suggest the transmission of TEN infection through sexual contact. Local transmission of the macrolide-resistant TEN strains is suspected, and the expansion to a wide range of age groups via non-venereal mode of transmission is concerned. Recent findings on cases with a molecular diagnosis revealed that the epidemiological and clinical features of TEN infection are beyond the classical description. Since the clinical and laboratory features of TEN infection are indistinguishable from those of TPA infection [3–5], the molecular surveillance of syphilis will provide a more detailed understanding of the clinical manifestations of TEN infection outside of the classical hot spots, and will lead to the early control of the local transmission of TEN.

4. Ethics statement

The present study was approved by the Ethics Review Board of the Osaka Institute of Public Health (approval no. 0810-05-4). Specimens were collected primarily for the purpose of diagnosing *T. pallidum* infection. A molecular epidemiological study on *T. pallidum* was performed using residual specimens. All patients gave informed verbal consent prior to specimen collection by clinicians, which was documented in the medical records of the clinic.

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Authorship statement

All authors meet the ICMJE authorship criteria. All authors have contributed significantly to the work, and approved the final version of the manuscript. KS contributed with the original idea and case description, and wrote to the final version of the manuscripts with the help of KF, JK, and TK. YK, HM, and TK performed the bacteriological, molecular and genomic analyses.

Declaration of competing interest

Dr. Keiichi Furubayashi reports research expenses from SEKISUI MEDICAL CO., LTD. during the conduct of the study. The other authors declare they have no competing interests.

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References

[1] Giacani L, Lukehart SA. The endemic treponematoses. Clin Microbiol Rev 2014;27:89–115.

[2] Ahmed SS, Winslow DL. Endemic treponematoses. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. ninth ed. Philadelphia, PA: Elsevier; 2020. p. 2893–7.
[3] Grange PA, Allix-Beguec C, Chanal J, Benhaddou N, Gerhardt P, Morini JP, et al. Molecular subtyping of Treponema pallidum in paris, France. Sex Transm Dis 2013; 40:641–4.
[4] Grange PA, Mikalová L, Gaudin C, Strouhal M, Janier M, Benhaddou N, et al. Treponema pallidum 11qj subtype may correspond to a Treponema pallidum subsp. Endemicum strain. Sex Transm Dis 2016;43:517–8.
[5] Noda AA, Grillová L, Lienhard R, Blanco O, Rodríguez I, Šmajs D. Bejel in Cuba: molecular identification of Treponema pallidum subsp. Endemicum in patients diagnosed with venereal syphilis. Clin Microbiol Infect 2018;24:1210.e1–5.
[6] Kawahata T, Kojima Y, Furubayashi K, Shinohara K, Shimizu T, Komano J, et al. Bejel, a nonvenereal treponematosis, among men who have sex with men, Japan. Emerg Infect Dis 2019;25:1581–3.
[7] Kojima Y, Furubayashi K, Kawahata T, Mori H, Komano J. Circulation of distinct Treponema pallidum strains in individuals with heterosexual orientation and men who had sex with men. J Clin Microbiol 2019;57. e01148-18.
[8] Yakinci C, Ozcan A, Aslan T, Demirhan B. Bejel in Malatya, Turkey. J Trop Pediatr 1995;41:117–20.
[9] Fanella S, Kadkhoda K, Shuel M, Tsang R. Local transmission of imported endemic syphilis, Canada, 2011. Emerg Infect Dis 2012;18:1002–4.
[10] Abdolrasouli A, Croucher A, Hemmati Y, Mabey D. A case of endemic syphilis, Iran. Emerg Infect Dis 2013;19:162–3.
[11] Farnsworth N, Rosen T. Endemic treponematosis: review and update. Clin Dematol 2006;24:181–90.
[12] Lipozenčić J, Marinović B, Gruber F. Endemic syphilis in Europe. Clin Dermatol 2014;32:219–26.
[13] Hudson EH. Bejel: the endemic syphilis of the Euphrates Arab. Trans R Soc Trop Med Hyg 1937;31:9–46.
[14] Akrawi F. Is bejel syphilis? Br J Vener Dis 1949;25:115–23.
[15] Lukehart SA, Godornes C, Molini BJ, Sonnett P, Hopkins S, Mulcahy F, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. N Engl J Med 2004;351:154–8.
[16] Matějková P, Flasarová M, Zákoucká H, Bořek M, Křemenová S, Arenberger P, et al. Macrolide treatment failure in a case of secondary syphilis: a novel A2059G mutation in the 23S rRNA gene of Treponema pallidum subsp. Pallidum J Med Microbiol 2009;58:832–6.
[17] Šmajs D, Paštěková L, Grillová L. Macrolide resistance in the syphilis spirochete, Treponema pallidum ssp. pallidum: Can we also expect macrolide-resistant yaws strains? Am J Trop Med Hyg 2015;94:678–83.
[18] Mitjà O, Godornes C, Houinei W, Kapa A, Paru R, Abel H, et al. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. Lancet 2018;391:1599–607.