Original Research Article

Chlamydial Proctitis in patients with Chlamydial Cervicitis

Abstract

Aims:We investigated the status of chlamydial proctitis, detected using a transcription-mediated amplification (TMA) method, in rectal mucosal swab samples from patients with chlamydial cervicitis.

Methodology: Patients with chlamydial cervicitis were interviewed, and rectal mucosal swab samples were collected for TMA. If the patient agreed, colonoscopy was also conducted. Chlamydial proctitis was treated with a single dose of oral azithromycin (2000 mg). Three weeks after treatment, additional samples from the cervix and rectal mucosa were subjected to TMA, and follow-up colonoscopy was performed.

Results: Among the 59 patients, 4 had diarrhea and 3 had melena; only 1 patient had practiced anal sex. The rectal mucosal TMA test was positive in 43 (72.9%) cases. After treatment, TMA tests of the cervix and rectal mucosa were negative in all patients and in 26 (86.7%) of 30 patients, respectively.

Conclusion:The clearance rate of chlamydial infection of the rectal mucosa was not 100% and the cervical samples became negative in all cases following treatment in this study. Further studies may be needed to determine the optimal indicator for evaluating patient treatment responses and to reliably clear the infection with an alternate drug or dosing regimen.

Key words:Chlamydialproctitis; Chlamydial cervicitis; Azithromycin; Transcription-mediated amplification.

1. Introduction

Globally, chlamydial infections are the most frequent type of sexually transmitted disease, and its high prevalence poses a social problem in Japan. Gynecological and obstetric diseases arising from this infection, such as cervicitis, uterine adnexitis, and pelvic inflammatory disease, may cause both ectopic pregnancies and tubal infertility. In addition, the infection may lead to other conditions requiring care, including (1) care at a critical care unit because of emergent conditions, such as perihepatitis or ileus due to adhesions; (2) care at departments of internal medicine or surgery; (3) pediatric care of neonates with inclusion conjunctivitis or pneumonia caused by transmission from the mother during labor; (4) care of male urethritis and epididymitis at a urology department; (5) care of pharyngeal infections arising from oral sex, reflecting recent changes in sexual habits; and (6) care of infectious bowel disease due to chlamydia (a recently highlighted condition). Thus, chlamydial infections present with extensive clinical signs that require care by both specialties traditionally associated with chlamydial infection treatment (obstetrics, gynecology, and urology), and additional medical specialties, including internal medicine, pediatrics, ophthalmology, and otorhinolaryngology. *Chlamydia trachomatis*, which primarily infects the urethra and uterine cervix, is known to have the potential for infecting the palpebral conjunctiva, pharynx, and rectum, which are composed of columnar epithelia [1].

Chlamydial proctitis was first reported in 1981 by Quinn et al. [2] and has been reported in Western countries primarily among homosexuals [3,4] since the 1980s; such cases have also recently been reported in Japan. The symptoms are melena, abdominal pain, diarrhea, or mucous/bloody stool, therefore, most of these reports have been made by gastroenterologists, with few being made by obstetricians and gynecologists. The present study was undertaken to investigate the status of chlamydial proctitis, detected using a transcription-mediated amplification (TMA) method, in samples collected from the rectal mucosa of patients with chlamydial cervicitis, and we discussed the possible causes, clinical symptoms,

colonoscopicfindings, and TMA results after treatment of rectal infection.

2. Material and Methods

Between 2010 and 2012, we investigated patients with chlamydial cervicitis at Kyoto Prefectural University of Medicine Hospital and at the Hoshina sexually transmitted disease clinic.The diagnosis of chlamydia cervicitis was confirmed using the nucleic acid amplification (polymerase chain reaction) method. The 59 patients with chlamydial cervicitis were interviewed to determine age, occupation, marital status (married/unmarried), and the presence/absence of abdominal pain, diarrhea, mucous/bloody stool, melena, superficial lymph node swelling, and participation in anal sex. To collect samples, the skin around the anus was cleaned, and a sample of the rectal mucosa was collected with a swab. Each sample was tested using the APTIMA™ Combo 2 Chlamydia/GonorrhoeaeTMA method (Hologic Gen-Probe, San Diego, CA, USA). In patients with a positive rectal mucosal TMA test, a colonoscopy was conducted to check for rectal lesions if the patient agreed. Chlamydial proctitis, if detected, was treated with a single dose of oral azithromycin (AZM, Zithromax SR®, 2000 mg, Pfizer, New York City, NY, USA).Japanese Society for Sexually Transmitted Infections recommends single-dose treatment with 4 tablets of 250mg Zithromax® (1000mg), or 2000 mg Zithromax SR®dry syrup for chlamydial infections. Three weeks after treatment, a repeat TMA test was conducted on samples collected from the uterine cervix and rectal mucosa.The patients co-infected with *Neisseria gonorrhoeae* simultaneously received a single dose of intravenous ceftriaxone sodium (CTRX, Rocephin®, 1000mg, Roche Pharmaceuticals, South San Francisco, CA, USA).

Statistical examinations of the outpatients and commercial sex workers (CSWs) were performed using Mann-Whitney's *U*-test and chi-square test with Yates' correction.

3. Results

The 59 patients with chlamydial cervicitis, enrolled in this study, were 18-44-years-old (mean, 26.2-years-old). There were no significant differences between patients treated on an outpatient basis and those who were CSWs. The reported occupations of the patients were CSW (43), female office worker (8), student (5), and housewife (3). Of the 16 non-CSW patients, 15 were unmarried and 1 was married. None of the patients reported abdominal pain or mucous/bloody stool. Diarrhea was reported by 4 patients. Superficial lymph node swellings were not detected in any of the patients. Only 1 patient reported practicing anal sex.

The rectal mucosal TMA tests were positive in 43 (72.9%) of the 59 patients with cervicitis. Although the ratio was higher among the outpatients (13/16, 81.3%) than among the CSWs (30/43, 69.8%), the difference was not statistically significant($P = 0.382$). Six (10.2%) of the patients were positive for *N.gonorrhoeae*; none of the outpatients and 6/43 (14.0%) of the CSWs were gonorrhea-positive.Among the 6 patients, the follow-up TMA test 3 weeks after CTRX administration was negative for *N. gonorrhoeae* in all cases.

Of the 43 patients with a positive rectal mucosa TMA test, 30 (69.8%) returned to the facility on the appointed date, after treatment. The consultation rate was not significantly different between the general outpatients (9/13, 69.2%) and the CSWs (21/30, 70%). Among the patients retested after treatment, the test was negative in 26 patients (eradication rate, 86.7%). There was no significant difference in the bacterial eradication rate between the general outpatients (9/9, 100%) and the CSWs (17/21, 81%). Among the 26 patients testing negative after AZM treatment, all cervical samples were also negative, according to the TMA test.

Fig. 1.shows the typical lower intestinal colonoscopy findings, prior to and after AZM treatment, in patients with positive TMA chlamydial results; revealing marked alleviation of the multiple white elevation lesions of rectal mucosa.

4. Discussion

The first reported Japanese case of chlamydial proctitis occurred in an 18-year-old woman. Her

chief complaints were hypogastric pain and mucous/bloody stool. The endoscopic findings of her rectal mucosa resembled ikura (salmon roe), and her rectal mucosa brush cytology was positive for the chlamydia antigen. The case report indicated the possibility that chlamydial proctitis needs to be considered in the differential diagnosis of infectious enteritis. In the intervening years, until 2012, only 38 cases of this condition were reported. The small number of reported cases of this disease may be attributed to the fact that many patients with this condition may remain undetected because the symptoms are mild and that the rectal mucosal brush cytology that is used for the detection of chlamydia is not covered by Japanese national health insurance and is therefore less frequently performed.Among the 38 reported cases of this disease, to date, symptoms of melena, abdominal pain, diarrhea, and mucous/bloody stool were observed in some cases, but asymptomatic cases were not uncommon. In the present study, involving 59 patients with cervicitis, diarrhea was seen in 4 patients and melena was seen in 3, but abdominal pain, mucous/bloody stool, and superficial lymph node swellings were absent in all cases. Sexually active females presenting with rectal pain and complaints should be screened for *C. trachomatis* infection of the rectum [5].

The rectal mucosal sample TMA tests were positive in 43 (72.9%) of the 59 patients with cervicitis. This result, from a small number of subjects, suggests that the chlamydia detection rate in rectal mucosa is high among patients with cervicitis, although further studies are needed. Previous screenings of CSWs revealed that the prevalence of chlamydial proctitis ranged from 5.2% to 17.5% [6-8]. In the present study, among CSWs with chlamydial cervicitis, the prevalence of chlamydial proctitis was 69.8% (30/43). One of the previous screens of CSWs indicated that the prevalence of gonococcalproctitis was 13.4% (13/97), which was similar to the 14.0% (6/43) observed in the present study.

The diagnosis of chlamydial proctitis is possible using nucleic acid amplification, which is a test that has excellent sensitivity and specificity and that is conventionally used for the diagnosis of genital chlamydial infections. The present study used the APTIMA™ Combo 2

Chlamydia/Gonorrhoeae kit, which is able to simultaneously detect *C. trachomatis* and *N. gonorrhoeae*. With this kit, coexisting substances are first eliminated by the target-capture method, and nucleic acid amplification of the target gene (rRNA) is conducted (TMA) so that *C. trachomatis* and *N.gonorrhoeae* are simultaneously checked in the same test tube containing the same sample by means of a dual kinetic assay.The known routes of chlamydial infection of the rectum include: (1) direct invasion of the rectal mucosa during anal sex, (2) flow of infected vaginal secretions into the rectum through the anus (females), and (3) lymphogenous invasion of the rectum through the uterus, cervix, vagina, or urethra [2]. Considering that most of the female patients with this disease, to date, have reported no experience with anal sex and were free of superficial lymph node swelling, the flow of infected vaginal secretions into the rectum, through the anus, may be the major route of chlamydial rectal infection. Patients in the present study also reported the absence of experience with anal sex, further suggesting that secretions from the infected cervical region cause the rectal infection.

A characteristic endoscopic finding of rectums infected with chlamydia is the presence of small, hemispheric, and elevated lesions called “ikura-like” mucosa [9]. Endoscopy of one of the typical cases, in the present study, revealed a group of small, white, hemispheric elevations that were confined to the rectal mucosa (ikura-like mucosa), reflecting lymph follicle hyperplasia.

Of the 43 patients whose rectal mucosal samples were positive in the TMA tests, 30 (69.8%) visited the facility on the appointed date after treatment. The percentage of patients with chlamydial cervicitis who attend follow-up consultations has been reported to be 66%, which is significantly lower than the rate for patients free of chlamydial infection (93.9%). This low revisit rate has been identified as a serious problem contributing to the poor treatment and spread of the infection [10]. However, in the present study, the revisit rate was equal to the reported follow-up rate.

The recommended treatment for genital chlamydial infections involves either single-dose AZM (1000 mg) or 7-day clarithromycin (400 mg) oral treatment [10]. Although reports describing

the recommended drugs and dosing period for treating chlamydial proctitis are not available, alleviation of the disease following 14-day to 2-month clarithromycin (400 mg) treatment has been shown [11]. In the present study, rectal mucosa TMA tests demonstrated that the patients became negative for the presence of chlamydia after treatment with single-dose, 2000-mg AZM in 26 of the 30 cases (eradication rate, 86.7%). In these 30 cases, the cervical samples also became negative in the TMA test. Thus, successful treatment of chlamydial cervicitis was possible in all cases following AZM treatment with a chlamydial proctitis cure rate of 86.7%. Some cases of rectal chlamydial infections may require prolonged treatment, as is also required for chlamydial infections of the pharynx.

According to a previous study on the distribution of radiolabeled AZM in rats, drug levels in large bowel tissue were about 20 times higher than serum drug levels, and the levels were increased further in infected areas because AZM is taken up by neutrophils and accumulates to high levels in areas of infection [12]. The maximum concentration of AZM was reported to be approximately 25 μg/mL in colorectal tissue (1.24 μg/mL in serum of healthy adults), with a 24-h area under the serum concentration-time curve (AUC) of approximately 190 μg/mL in colorectal tissue (9.39 μg/mL in serum of healthy adults) [13]. Because the minimal inhibitory concentration of AZM against *C. trachomatis* is 0.063 to 0.125 μg/mL, the drug levels in the affected tissues are sufficiently high.

Like the healing of genital chlamydial infections, the healing of chlamydial proctitis is judged based on polymerase chain reaction results, and other methods, that are conducted 3-4 weeks after the start of treatment. In the future, the collection of data from additional cases is desirable to determine the optimum treatment and the optimal indicator for evaluating patient treatment responses.It has been verified that a single testat 3-8 weeks following single-dose AZM treatment for anorectal and cervicovaginal*C. trachomatis*infections frequently misses its detection [14] and that test-of-cure cannot be based on a single highly sensitive laboratory test taken at least 3 weeks after treatment [15].In this study, single-dose treatment with AZM (2000

mg) resulted in endoscopic improvements in our patients. At present, however, there is no widely accepted regimen for the dose or dosing regimen; further studies are needed to establish theseguidelines.For the time being, the Guidelines on the Diagnosis and Treatment of Sexually Transmitted Diseases [11] should be referenced when dealing with cases of chlamydial proctitis. Chlamydial proctitis is probably often overlooked, clinically, because its symptoms are mild. The route of transmission of this disease is sometimes unknown, but active therapeutic intervention should be taken for the patient as well as for the patient's partner. The possibility of chlamydial infection needs to be considered, when diagnosis and treating unexplained proctitis.

5. Conclusion

The clearance rate of chlamydial infection of the rectal mucosa was not 100% (eradication rate, 86.7%) and the cervical samples became negative in all cases following AZM treatment in this study. Further studies may be neededto determine the optimal indicator for evaluating patient treatment responses and to reliably clear the infection with an alternate drug or dosing regimen.

CONSENT

All patients gave written informed consent before participation.

ETHICAL APPROVAL

This study was approved by the Kyoto Prefectural University of Medicine medical ethics screening committee (ERB-C-27).

References

1.Iwasaku K.Pelvic infection 1. Chlamydial infection-Essential points in diagnosis of infection revealed by analysis of individual cases (supervised by Shinagawa T., edited by Takeyama H.). Iyaku Journal.2005;146-50. Japanese.

208 2.Quinn TC,Goodell SE, Mkrtichian E, Schuffler MD, Wang SP, Stamm WE, et al.Chlamydia
209 trachomatis proctitis. N Engl J Med. 1981;305(4):195-200. PUBMED ID:7017409.
210 3.Jin F, Prestage GP, Mao L, Kippax SC, Pell CM, Donovan B, et al. Incidence and risk factors
211 for urethral and anal gonorrhoea and chlamydia in a cohort of HIV-negative homosexual men:
212 the Health in Men Study. Sex Transm Infect. 2007;83(2):113-9.DOI:10.1136/sti.2006.021915.
213 PUBMED ID:17005541.
214 4.Lister NA, Smith A, Tabrizi S, Hayes P, Medland NA, Garland S, et al. Screening for
215 Neisseria gonorrhoeae and Chlamydia trachomatis in men who have sex with men at male-only
216 saunas.Sex Transm Dis. 2003;30(12):886-9. PUBMED ID:14646635.
217 5.Solomon ML, Middleman AB. Abdominal pain, constipation, and tenesmus in an adolescent
218 female: consider Chlamydia proctitis. J Pediatr Adolesc Gynecol. 2013;26(3):e77-9. DOI:
219 10.1016/j.jpag.2013.01.003. PUBMED ID: 23518359.
220 6.Hunte T, Alcaide M, Castro J. Rectal infections with chlamydia and gonorrhoea in women
221 attending a multiethnic sexually transmitted diseases urban clinic. Int J STDAIDS.
222 2010;21(12):819-22. DOI: 10.1258/ijsa.2010.009279. PUBMED ID: 21297090.
223 7.Sethupathi M, Blackwell A, Davies H. Rectal Chlamydia trachomatis infection in women. Is it
224 overlooked?.Int J STD AIDS.2010;21(2):93-5. DOI: 10.1258/ijsa.2008.008406. PUBMED ID:
225 19917639.
226 8.Thompson CI, MacAulay AJ, Smith IW. chlamydia trachomatis infections in the female
227 rectums. Genitourin Med. 1989;65(4):269-73. PUBMED ID: 2807287.
228 9.Iwasaku K, Kitawaki J. Chlamydial Proctitis.Japanese Journal of Sexually Transmitted
229 Diseases. 2011;22(1):146-50.Japanese.
230 10.Iwasaku K, Takano K, Shimozato C, Yoneda S, Matsumura Y.Clinical analysis of
231 chlamydial cervicitis in Kyoto City Hospital. Japanese Journal of Sexually Transmitted
232 Diseases. 2007;18(1):89-96.Japaneses.
233 11.U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, Centers for Disease

Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Sexually Transmitted Disease Surveillance 2011.Division of STD Prevention, December 2012.

12. Muto H, Kuboe Y, Kimura Y, et al. Pharmacokinetics study of azithromycin in experimental animals. Jpn J Chemother. 1995;43(Suppl. 6):110-21. Japanese.

13.Package insert for Zithromax SR. Available: http://www.info.pmda.go.jp/downfiles/ph/PDF/671450_6149004R1024_2_03.pdf

14.Dukers-Muijrers NH, Speksnijder AG, Morré SA, Wolffs PF, van der Sande MA, Brink AA, et al. Detection of anorectal and cervicovaginal Chlamydia trachomatis infections following azithromycin treatment: prospective cohort study with multiple time-sequential measures of rRNA, DNA, quantitative load and symptoms. PLoS One. 2013;8(11):e81236. DOI: 10.1371/journal.pone.0081236. PUBMED ID:24278400.

15.Dukers-Muijrers NH, Morré SA, Speksnijder A, van der Sande MA, Hoebe CJ. Chlamydia trachomatis test-of-cure cannot be based on a single highly sensitive laboratory test taken at least 3 weeks after treatment. PLoS One. 2012;7(3):e34108. DOI: 10.1371/journal.pone.0034108. PUBMED ID:22470526.

Figure legend

Fig. 1.Representative lower intestinal endoscopic findings of rectum in a patient with chlamydial proctitis, by courtesy of Dr. Takashi Ando (Director, Department of Gastroenterology, Social Insurance Kyoto Hospital). Pretreatment endoscopy revealed multiple, white elevations in the rectum. The lesions were pathologically rated as multiple lymphoid follicles (A-C). After azithromycin treatment, rectal endoscopy revealed marked alleviation, although slightly elevated lesions remained (D-F).

259 Fig. 1.

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