

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 possible, colonoscopy was also conducted. Chlamydial proctitis was treated with a single dose of oral azithromycin (2000 mg). 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: Among the 59 patients with chlamydial cervicitis, 43 (72.9%) also had chlamydial infection of the rectal mucosa. Although 26 of 30 patients who were treated and then presented for follow-up were cleared of their infection, the absence of a 100% clearance rate suggests the possible need for an alternate drug or dosing regimen to reliably clear the infection.

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

26 1. Introduction

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

44 Chlamydial proctitis was first reported in 1981 by Quinn et al. [2] and has been reported in
45 Western countries primarily among homosexuals [3,4] since the 1980s; such cases have also
46 recently been reported in Japan. Most of these reports have been made by gastroenterologists,
47 with few being made by obstetricians and gynecologists. The present study was undertaken to
48 investigate the characteristics of chlamydial proctitis using samples collected from the rectal
49 mucosa of patients with chlamydial cervicitis.

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51 2. Material and Methods

52 Between 2010 and 2012, we investigated patients with chlamydial cervicitis at Kyoto
53 Prefectural University of Medicine Hospital and at the Hoshina sexually transmitted disease
54 clinic. The diagnosis of chlamydia cervicitis was confirmed using the nucleic acid amplification
55 (polymerase chain reaction) method. The 59 patients with chlamydial cervicitis were
56 interviewed to determine age, occupation, marital status (married/unmarried), and the
57 presence/absence of abdominal pain, diarrhea, mucous/bloody stool, melena, superficial lymph
58 node swelling, and participation in anal sex. To collect samples, the skin around the anus was
59 cleaned, and a sample of the rectal mucosa was collected with a swab. Each sample was tested
60 using the APTIMA™ Combo 2 Chlamydia/Gonorrhoeae transcription-mediated amplification
61 (TMA) method (Hologic Gen-Probe, San Diego, CA, USA). In patients with a positive rectal
62 mucosal TMA test, a colonoscopy was generally conducted to check for rectal lesions.
63 Chlamydial proctitis, if detected, was treated with a single dose of oral azithromycin (AZM,
64 Zithromax SR®, 2000 mg, Pfizer, New York City, NY, USA). Three weeks after treatment, a
65 repeat TMA test was conducted on samples collected from the uterine cervix and rectal mucosa.
66 Statistical examinations of the outpatients and commercial sex workers (CSWs) were performed
67 using Student's *t*-test and Fischer's direct probability.

68

69 3. Results

70 The 59 patients with chlamydial cervicitis, enrolled in this study, were 18-44-years-old (mean,
71 26.2-years-old). There were no significant differences between patients treated on an outpatient
72 basis and those who were CSWs. The reported occupations of the patients were CSW (43),
73 female office worker (8), student (5), and housewife (3). Of the 16 non-CSW patients, 15 were
74 unmarried and 1 was married. None of the patients reported abdominal pain or mucous/bloody
75 stool. Diarrhea was reported by 4 patients. Superficial lymph node swellings were not detected
76 in any of the patients. Only 1 patient reported practicing anal sex.
77 The rectal mucosal TMA tests were positive in 43 (72.9%) of the 59 patients with cervicitis.

78 Although the ratio was higher among the outpatients (13/16, 81.3%) than among the CSWs
79 (30/43, 69.8%), the difference was not statistically significant. Six (10.2%) of the patients were
80 positive for *Neisseria gonorrhoeae*; none of the outpatients and 6/43 (14.0%) of the CSWs
81 were gonorrhea-positive.

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

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

92

93 4. Discussion

94 The first reported Japanese case of chlamydial proctitis occurred in an 18-year-old woman. Her
95 chief complaints were hypogastric pain and mucous/bloody stool. The endoscopic findings of
96 her rectal mucosa resembled ikura (salmon roe), and her rectal mucosa brush cytology was
97 positive for the chlamydia antigen. The case report indicated the possibility that chlamydial
98 proctitis needs to be considered in the differential diagnosis of infectious enteritis. In the
99 intervening years, until 2012, only 38 cases of this condition were reported. The small number
100 of reported cases of this disease may be attributed to the fact that many patients with this
101 condition may remain undetected because the symptoms are mild and that the rectal mucosal
102 brush cytology that is used for the detection of chlamydia is not covered by Japanese national
103 health insurance and is therefore less frequently performed. Among the 38 reported cases of this

104 disease, to date, symptoms of melena, abdominal pain, diarrhea, and mucous/bloody stool were
105 observed in some cases, but asymptomatic cases were not uncommon. In the present study,
106 involving 59 patients with cervicitis, diarrhea was seen in 4 patients and melena was seen in 3,
107 but abdominal pain, mucous/bloody stool, and superficial lymph node swellings were absent in
108 all cases. Sexually active females presenting with rectal pain and complaints should be screened
109 for *C. trachomatis* infection of the rectum [5].

110 The rectal mucosal sample TMA tests were positive in 43 (72.9%) of the 59 patients with
111 cervicitis. This result, from a small number of subjects, suggests that the chlamydia detection
112 rate in rectal mucosa is high among patients with cervicitis, although further studies are needed.
113 Previous screenings of CSWs revealed that the prevalence of chlamydial proctitis ranged from
114 5.2% to 17.5% [6-8]. In the present study, among CSWs with chlamydial cervicitis, the
115 prevalence of chlamydial proctitis was 69.8% (30/43). One of the previous screens of CSWs
116 indicated that the prevalence of gonococcal proctitis was 13.4% (13/97), which was similar to
117 the 14.0% (6/43) observed in the present study.

118 The diagnosis of chlamydial proctitis is possible using nucleic acid amplification, which is a test
119 that has excellent sensitivity and specificity and that is conventionally used for the diagnosis of
120 genital chlamydial infections. The present study used the APTIMA™ Combo 2
121 Chlamydia/Gonorrhoeae kit, which is able to simultaneously detect *C. trachomatis* and *N.*
122 *gonorrhoeae*. With this kit, coexisting substances are first eliminated by the target-capture
123 method, and nucleic acid amplification of the target gene (rRNA) is conducted (TMA) so that *C.*
124 *trachomatis* and *N.gonorrhoeae* are simultaneously checked in the same test tube containing the
125 same sample by means of a dual kinetic assay. The known routes of chlamydial infection of the
126 rectum include: (1) direct invasion of the rectal mucosa during anal sex, (2) flow of infected
127 vaginal secretions into the rectum through the anus (females), and (3) lymphogenous invasion
128 of the rectum through the uterus, cervix, vagina, or urethra [2]. Considering that most of the
129 female patients with this disease, to date, have reported no experience with anal sex and were

130 free of superficial lymph node swelling, the flow of infected vaginal secretions into the rectum,
131 through the anus, may be the major route of chlamydial rectal infection. Patients in the present
132 study also reported the absence of experience with anal sex, further suggesting that secretions
133 from the infected cervical region cause the rectal infection.

134 A characteristic endoscopic finding of rectums infected with chlamydia is the presence of small,
135 hemispheric, and elevated lesions called “ikura-like” mucosa [9]. Endoscopy of one of the
136 typical cases, in the present study, revealed a group of small, white, hemispheric elevations that
137 were confined to the rectal mucosa (ikura-like mucosa), reflecting lymph follicle hyperplasia.
138 Of the 43 patients whose rectal mucosal samples were positive in the TMA tests, 30 (69.8%)
139 visited the facility on the appointed date after treatment. The percentage of patients with
140 chlamydial cervicitis who attend follow-up consultations has been reported to be 66%, which is
141 significantly lower than the rate for patients free of chlamydial infection (93.9%). This low
142 revisit rate has been identified as a serious problem contributing to the poor treatment and
143 spread of the infection [10]. However, in the present study, the revisit rate was equal to the
144 reported follow-up rate.

145 The recommended treatment for genital chlamydial infections involves either single-dose AZM
146 (1000 mg) or 7-day clarithromycin (400 mg) oral treatment [10]. Although reports describing
147 the recommended drugs and dosing period for treating chlamydial proctitis are not available,
148 alleviation of the disease following 14-day to 2-month clarithromycin (400 mg) treatment has
149 been shown [11]. In the present study, rectal mucosa TMA tests demonstrated that the patients
150 became negative for the presence of chlamydia after treatment with single-dose, 2000-mg AZM
151 in 26 of the 30 cases (eradication rate, 86.7%). In these 30 cases, the cervical samples also
152 became negative in the TMA test. Thus, successful treatment of chlamydial cervicitis was
153 possible in all cases following AZM treatment with a chlamydial proctitis cure rate of 86.7%.
154 Some cases of rectal chlamydial infections may require prolonged treatment, as is also required
155 for chlamydial infections of the pharynx.

156 According to a previous study on the distribution of radiolabeled AZM in rats, drug levels in
157 large bowel tissue were about 20 times higher than serum drug levels, and the levels were
158 increased further in infected areas because AZM is taken up by neutrophils and accumulates to
159 high levels in areas of infection [12]. The maximum concentration of AZM was reported to be
160 approximately 25 µg/mL in colorectal tissue (1.24 µg/mL in serum of healthy adults), with a
161 24-h area under the serum concentration-time curve (AUC) of approximately 190 µg/mL in
162 colorectal tissue (9.39 µg/mL in serum of healthy adults) [13]. Because the minimal inhibitory
163 concentration of AZM against *C. trachomatis* is 0.063 to 0.125 µg/mL, the drug levels in the
164 affected tissues are sufficiently high.

165 Like the healing of genital chlamydial infections, the healing of chlamydial proctitis is judged
166 based on polymerase chain reaction results, and other methods, that are conducted 3-4 weeks
167 after the start of treatment. In the future, the collection of data from additional cases is desirable
168 to determine the optimum treatment and the optimal indicator for evaluating patient treatment
169 responses. In this study, single-dose treatment with AZM (2000 mg) resulted in endoscopic
170 improvements in our patients. At present, however, there is no widely accepted regimen for the
171 dose or dosing regimen; further studies are needed to establish these guidelines. For the time
172 being, the Guidelines on the Diagnosis and Treatment of Sexually Transmitted Diseases [11]
173 should be referenced when dealing with cases of chlamydial proctitis.

174 Chlamydial proctitis is probably often overlooked, clinically, because its symptoms are mild.
175 The route of transmission of this disease is sometimes unknown, but active therapeutic
176 intervention should be taken for the patient as well as for the patient's partner. The possibility of
177 chlamydial infection needs to be considered, when diagnosis and treating unexplained proctitis.

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182 CONSENT

183 All patients gave written informed consent before participation.

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185 ETHICAL APPROVAL

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

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226 Figure legend

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

233

234 Fig. 1.

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