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Clinical relevance of nucleic acid amplification test for patients with urinary tuberculosis during antituberculosis treatment

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Abstract The nucleic acid amplification test (NAAT) has been valuable in the diagnosis of urinary tuberculosis; however, no studies have attempted to determine the significance of NAAT post treatment. We encountered three patients with urinary tuberculosis who underwent sequential NAAT during antituberculosis chemotherapy and post treatment. All patients were diagnosed as having urinary tuberculosis by positive NAAT and specific renal deformity revealed by imaging. In two of the three patients, positive culture results were obtained and one was negative in standard culture. During antituberculosis chemotherapy, a negative NAAT was obtained from 3 to 5 months after the start of treatment and no positive culture results were obtained during the same period. At the end of chemotherapy, 6 months or more after the start of medication, all patients had negative NAAT results. These results suggest that NAAT for *Mycobacterium tuberculosis* provides an effective and rapid detection method for urinary tuberculosis both pre- and post-treatment.

Key words Urinary tuberculosis · Nucleic acid amplification test · *Mycobacterium tuberculosis*

Urinary tuberculosis is now a rare disease, and urologists have difficulty with its diagnosis because some patients with urinary tuberculosis have no specific symptoms. Acid-fast bacilli (AFB) stain, one of the detection methods, is relatively easy to perform; however, it has lower sensitivity to detect *Mycobacteria tuberculosis* than culture methods.[1] Culture remains the gold standard to detect *M. tuberculosis* and it can demonstrate the sensitivity of various antituberculosis drugs. However, we often need several weeks to clearly detect its colonies by culture.

In recent years, the nucleic acid amplification test (NAAT) kit has been widely used for the detection for various microorganisms because of its higher sensitivity and specificity. There have been several reports that urinary NAAT for *M. tuberculosis* has an effective and important role in its diagnosis.[1–3] We determined that NAAT had an important role in not only the diagnosis but also in the follow-up of patients with urinary tuberculosis.

The subjects in this study were three patients with urinary tuberculosis. Case 1 was a 79-year-old woman who visited our clinic for pollakisuria and pain on micturition. She had pyuria but no isolated urinary pathogen determined by urine culture. Although she was medicated with oral quinolone and cephalosporin, her voiding symptoms recurred repeatedly. In addition, her urinary sediment showed pyuria and microscopic hematuria intermittently. Therefore, examinations of urinary cytology and a commercially available nucleic acid amplification test (NAAT) for *M. tuberculosis* were ordered. The result of urinary cytology was negative; however, NAAT was positive for *M. tuberculosis* in the urine sample. *Escherichia coli* was also isolated from the urine sample at the same time. Based on the result of NAAT, a urine sample was cultured and *M. tuberculosis* was isolated using 3% Ogawa Medium (Kyokuto Pharmaceutical Industrial, Tokyo, Japan). The sensitivity for most antituberculous drugs was excellent and no multidrug-resistant isolates were found. An imaging test revealed a small nodule in her lung but no discharge of *M. tuberculosis* organisms was confirmed by a specialist in respiratory diseases. No abnormal findings in the spine were found by imaging. Intravenous pyelography and computed tomography (CT) revealed deformities in the right upper calices and normal renal function. Therefore she was diagnosed as having right renal tuberculosis. She was treated with isoniazid (INH) and rifampicin (RFP) for 6 months, and streptomycin (SM) for 2 months. No major adverse effects were observed from the start of medication. Culture and NAAT for *M. tuberculosis* were performed every month after the

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beginning of the treatment. The result of urine culture continued to be negative; however, NAAT was positive until 3 months after the beginning of medication. From 4 months after the start of medication, the results of NAAT were negative.[4]

Case 2 was a 60-year-old woman who visited our clinic for nocturia and discomfort in the right back. She had pyuria, which was refractory against regular antimicrobial chemotherapy for acute cystitis. No uropathogen was isolated. NAAT was performed for a urine sample and a positive result for *M. tuberculosis* was obtained. No abnormal findings were observed in her lung and spine by imaging. Intravenous pyelography showed dilation of the right calices and slightly decreased right renal function. Computed tomography also showed the same findings and a thick right ureteral wall. The results of culture were negative. She was diagnosed as having right renal and ureteral tuberculosis. She was medicated using four antituberculous drugs, INH and RFP for 6 months, pyrazinamide for 2 months, and SM for 1 month. She felt dizziness 1 month after the start of treatment. Although an otolaryngologist found no abnormality, SM was changed to ethambutol (EB) and the symptoms gradually improved. Ethambutol was administered for 1 month. Culture and NAAT for *M. tuberculosis* were performed every 1 month after beginning of the treatment. The results of NAAT were positive at 4 months after the beginning of medication and became negative at 5 months. No positive change was observed after treatment.

Case 3 was a 56-year-old man who visited our clinic for pain on micturition and pollakisuria. He had pyuria, and CT showed calcification in the left renal cortex. At first, antimicrobial chemotherapy was performed as for urethritis; however, the symptoms, including pyuria, did not improve. No uropathogen was isolated. NAAT for *M. tuberculosis* in urine sample was performed and proved positive for *M. tuberculosis*. No abnormal findings were found in the lungs and spine by imaging. Urine culture for *M. tuberculosis* was positive only in pretreatment examination. Intravenous pyelography showed slight deformity with calcification in the left middle renal calyx. The patient was diagnosed as having left renal tuberculosis. Treatment with four antituberculous drugs, INH, and EB was performed for 6 months. Rifampicin was administered for 2 months; however, it had to be changed to levofloxacin because of liver dysfunction. Levofloxacin was administered for 2 months, but was stopped because of mild renal dysfunction. Pyrazinamide was administered for 1 month. However, it had to be discontinued due to mild liver dysfunction. Culture and NAAT for *M. tuberculosis* were preformed every 1 month after the beginning of the treatment. The results of NAAT were positive at 5 months after the start of medication and became negative at 6 months. His renal and liver functions normalized post treatment.

At present, urinary tuberculosis is a rare disease. The number of newly diagnosed patients was approximately 150 in 2003, as was reported by the Japan Antituberculosis Association. This means that the frequency of urinary tuberculosis was approximately 0.5% of all tuberculosis cases. However, urinary tuberculosis is not yet negligible because no specific symptom is liable to be found and urologists have difficulties in diagnosing it. Therefore, a detection method is necessary for the diagnosis of urinary tuberculosis.

NAAT is widely used for microbiological detection and diagnosis in the field of infectious diseases. For the respiratory specimens, the sensitivity of NAAT is considerably less than that of culture,[5] although higher sensitivity in a large series was reported.[6,7] Indeed, the U.S. Food and Drug Administration announced that culture must be done in conjunction with the performance of each amplification-based test. In fact, in NAAT for the detection of *M. tuberculosis*, inhibiting substances have been detected in clinical samples at rates of from 1% to 20%. In diagnosis of genitourinary tuberculosis, polymerase chain reaction (PCR) for detection of urinary *M. tuberculosis* showed higher sensitivity and specificity in addition to rapid detection than the AFB stain or culture.[1,2] A report from Egypt revealed that the sensitivity and specificity of PCR assay were 95.6% and 98.1%, respectively.[1] A report from India demonstrated that PCR assay for detection of urinary *M. tuberculosis* was the most sensitive indicator among intravenous urography, bladder biopsy, and urine culture for AFB, and was positive in 94.3% of patients.[2] In our study, two patients were both culture- and PCR-positive for *M. tuberculosis*; however, one patient was only PCR positive. Although the nature of the PCR-positive and culture-negative state is unclear, the patient had specific renal pathology and symptoms. We speculated that the count of bacteria discharged from the affected site to urine might be low. NAAT for urinary *M. tuberculosis* provides an effective and rapid diagnostic test for urinary tuberculosis.

Generally, NAAT cannot distinguish between viable and nonviable organisms because nucleic acid, if it breaks into pieces, exists in the affected lesion for a long time after appropriate treatment. It is inevitable that a false-positive result be obtained by post-treatment NAAT in pulmonary tuberculosis[8] or for other pathogens.[9] Therefore, post-treatment sequential tests by NAAT might not be appropriate for judgment of a cure. It is reported that NAAT must not be used with patients on antituberculosis chemotherapy.[5] There have been few reports evaluating the significance of post-treatment NAAT for patients with urinary tuberculosis. In our study, the positive PCR results were found 3–5 months after the start of chemotherapy; however, no positive culture results were obtained during chemotherapy. This means that false-positive results can continue for 3–5 months after the start of chemotherapy. Thus, we would venture to suggest that close sequential NAAT is not necessary for patients with urinary tuberculosis. When NAAT is applied post treatment, the judgment of cure at the end of treatment, generally 6 months after the start of chemotherapy or more, might be suitable.

References

1. Moussa OM, Eraky I, El-Far MA, Osman HG, Ghoneim MA. Rapid diagnosis of genitourinary tuberculosis by polymerase chain

reaction and non-radioactive DNA hybridization. J Urol 2000;164: 584–8.
2. Hemal AK, Gupta NP, Rajeev TP, Dar RKL, Seth P. Polymerase chain reaction in clinically suspected genitourinary tuberculosis: comparison with intravenous urography, bladder biopsy, and urine acid fast bacilli culture. Urology 2000;56:570–4.
3. van Vollenhoven P, Heyns CF, de Beer PM, Whitaker P, van Helden PD, Victor HT. Polymerase chain reaction in the diagnosis of urinary tract tuberculosis. Urol Res 1996;24:107–11.
4. Takahashi S, Itoh N. A case of renal tuberculosis. J Med Assoc South Hokkaido 2000;35:341–3.
5. Piersimoni C, Scarparo C. Relevance of commercial amplification methods for direct detection of *Mycobacterium tuberculosis* complex in clinical samples. J Clin Microbiol 2003;41:5355–65.
6. Catanzaro AC, Perry S, Clarridge JE, Dunbar S, Goodnight-White S, LoBue PE, et al. The role of clinical suspicion in evaluating a new diagnostic test for active tuberculosis. Results of a multicenter prospective trial. JAMA 2000;283:639–45.
7. Çek M, Lenk S, Naber KG, Bishop MC, Johansen TE, Botto H, et al. EAU guidelines for the management of genitourinary tuberculosis. Eur Urol 2005;48:353–62.
8. Iinuma Y, Ichiyama S, Yamori S, Oohama J, Takagi N, Hasegawa Y, et al. Diagnostic value of the Amplicor PCR assay for initial diagnosis and assessment of treatment response for pulmonary tuberculosis. Microbiol Immunol 1998;42:281–7.
9. Takahashi S, Hagiwara T, Shiga S, Hirose T, Tsukamoto T. Detection of antimicrobial-treated *Chlamydia trachomatis* with Amplicor PCR test kit. J Infect Chemother 2000;6:211–5.