表 1　淋菌性尿道炎の治療

1．セフトリアキソン（CTRX：ロセフィン®）
　静注　1.0 g　単回投与
2．セフォジジム（CDZM：ケニセフ®，ノイセフ®）
　静注　1.0 g　単回投与
3．スペクチノマイシン（SPCM：トロビシン®）
　筋注　2.0 g　単回投与

〔文献 5）より引用〕

表 2　淋菌性咽頭感染の治療

1．セフトリアキソン（CTRX：ロセフィン®）
　静注　1.0 g　単回投与
2．セフォジジム（CDZM：ケニセフ®，ノイセフ®）
　静注　1.0 g または 2.0 g×1～2 回，1～3 日間投与

注）咽頭感染に対して，スペクチノマイシンの効果は劣るため使用すべきでない。セフトリアキソンの単回投与も経口セフェム耐性淋菌に対しては 100％の効果が得られない可能性があるので，投与後の検査は必須。淋菌が存続した場合でも，これらの薬剤の追加投与で除菌可能である。

〔文献 5）より引用〕

表 3　クラミジア性尿道炎の治療

1．アジスロマイシン（ジスロマック®）
　1 日　1,000 mg×1　1 日間
2．クラリスロマイシン（クラリス®，クラリシッド®）
　1 日　200 mg×2　7 日間
3．ミノサイクリン（ミノマイシン®）
　1 日　100 mg×2　7 日間
4．ドキシサイクリン（ビブラマイシン®）
　1 日　100 mg×2　7 日間
5．レボフロキサシン（クラビット®）
　1 日　100 mg×3　7 日間
6．トスフロキサシン（オゼックス®，トスキサシン®）
　1 日　150 mg×2　7 日間
7．ガチフロキサシン（ガチフロ®）
　1 日　200 mg×2　7 日間

〔文献 5）より引用〕

3 対処と処方の実際

顕微鏡下で双球菌の存在が確認できたならば，**表 1**[5]に示すように，「2006 年版性感染症診断・治療ガイドライン」で推奨されている薬剤を使用し，淋菌性尿道炎に対する治療を開始する。すべて注射による単回投与である。そして 1 週間後に必ず再診をするように患者に説明することが重要である。再診時にクラミジアの混合感染が認められたならば，**表 2**[5]に示すように，クラミジアに対する治療も開始する。さらに，咽頭からも淋菌が認められた場合，初診時の淋菌に対する治療が，セフトリアキソン以外で行われていれば，**表 3**[5]に示すように，セフトリアキソンの単回投与，あるいはセフォジジムの複数回の投与を追加しておくことが必要である。

最後に，淋菌性尿道炎の治療ガイドラインで推奨されている 3 薬剤に対しても，今後耐性化の可能性が否定できない。一方，現時点ではクラミジア性尿道炎の治療ガイドラインで推奨されている薬剤に対しての耐性菌の報告は極めて少ないものの，アジスロマイシン以外は 7 日間の内服継続が必要なため，患者の飲み忘れの危険性もある。

以上の点から，初診から数週間後に可能な限りもう一度受診をさせ，淋菌の除菌，および混合感染の際には，クラミジアの除菌の確認をすることが望ましい。

4 ここがポイント

感染の機会の有無，潜伏期間あるいは症状からのみで，淋菌とクラミジアとの混合感染を推測することは困難なので，初診時に必ずPCR法などによりクラミジアの有無を検査しておき，4〜7日後に必ず受診をさせ，クラミジアが陽性であった場合に初めてクラミジアに対する治療を開始することが重要である。

初期治療開始時に淋菌に対する治療と同時に，クラミジアに対する処方も行ってしまうのは，淋菌性尿道炎患者のうち混合感染をしていない70〜80%の患者に対して，まったく無意味な抗菌剤の投与となるので，医療安全上でも決して行うべきではないといえる[4]。

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NOTE

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Pharyngeal *Neisseria gonorrhoeae* detection in oral-throat wash specimens of male patients with urethritis

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Abstract Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in the pharynx has been highlighted in the prevention of the unexpected spread of sexually transmitted diseases. We tried to clarify the detection rate of *Neisseria gonorrhoeae* in the pharynx and the clinical relevance of oral-throat wash specimens to detect the organism in heterosexual men with gonococcal and nongonococcal urethritis. In our cohort of 79 male patients with urethritis, oral throat wash specimens were collected after they had gargled with normal saline for approximately 30 to 60 s. Positive pharyngeal *N. gonorrhoeae* was defined as a positive result on the strand displacement amplification test for the specimen from the oral-throat wash. *N. gonorrhoeae* was detected in the oral-throat wash specimens of 13 (31.7%) of the 41 male patients with gonococcal urethritis. Oral-throat wash with a nucleic acid amplification test can detect pharyngeal *N. gonorrhoeae* easily and efficiently.

Key words Oral-throat wash · Pharyngeal infection · *Neisseria gonorrhoeae* · *Chlamydia trachomatis* · Urethritis

Recently, several studies have reported an increasing detection rate for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in the pharynx in heterosexual men and women, which may be involved in the unrecognized spread of sexually transmitted diseases (STDs), because sexual behavior has been changing.[1,2] In general, pharyngeal gonococcal or chlamydial colonization or infection causes no specific symptoms.[2,3] Thus, screening and diagnostic procedures for detecting these organisms in the pharynx should be established promptly for the prevention of STD.

Pharyngeal swab specimens have generally been used for the detection of *N. gonorrhoeae* and *C. trachomatis* in the pharynx. In the clinical situation, however, it is always difficult to select the most appropriate areas to swab in the pharynx because infections by these organisms produce only nonspecific visible lesions. This may be one of the reasons why busy physicians are reluctant to routinely use the pharyngeal swab method in clinical practice.

The oral-throat wash method is an alternative to provide specimens that more efficiently detect pharyngeal *C. trachomatis*.[2] The use of this method has advantages for both patients and physicians because of the noninvasive nature of the test for patients and the simplicity of the procedure for physicians to obtain specimens. However, there have only been a few reports on the detection of pharyngeal *N. gonorrhoeae* in heterosexual men using specimens obtained by the oral-throat wash method.

In this context, we tried to clarify the detection rate of pharyngeal N. gonorrhoeae and the clinical relevance of the oral-throat wash method to detect the bacteria in the pharynx in heterosexual men with gonococcal urethritis.

Patients with urethritis were included in this study. They were heterosexual men and visited clinics complaining of typical symptoms such as pain on urination, urinary frequency, or pus discharge from the external urethral meatus. In addition, a white blood cell (WBC) count of 5/high-power field (hpf) or more was needed in the microscopic examination of the first voided urine sediments. Microbiological diagnosis was done by a polymerase chain reaction (PCR) test (Cobas Amplicor STD-1; Roche Diagnostic, Branchburg, NJ, USA) and diseases were classified as gonococcal urethritis (GU), nongonococcal and chlamydial urethritis (NGCU), and nongonococcal and nonchlamydial urethritis (NGNCU).

Oral-throat wash specimens were obtained according to a previously reported method,[2] which was partly modified. In brief, specimens were collected after the patients had gargled with 50 ml of normal saline for approximately 30 to 60 s. The specimens were divided into aliquots of 10 ml for

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the PCR test, 10 ml for the strand displacement amplification (SDA) test (BD ProbeTec ET CT/GC; BD Diagnostics, Sparks, MD, USA), 10 ml as a spare, and 20 ml for culture of *N. gonorrhoeae*. After centrifugation at 13000 g for 5 min, the precipitates of the specimens for culture were streaked onto modified Thayer-Martin agar[4] and incubated at 35°C for 48 h in a 5% CO_2 incubator. *N. gonorrhoeae* was identified using Gram's stain, an oxidase test, and the Gonochek-II Kit (EY Laboratories, San Mateo, CA, USA). Detection of pharyngeal *N. gonorrhoeae* was performed by using the specimens for PCR and SDA tests.

Pharyngeal *N. gonorrhoeae* was defined as positive when the results of the SDA test and/or culture were positive, because *Neisseria subflava* and *Neisseria cinerea*, both of which are normal bacterial flora in the pharynx, produce a positive result in the PCR test,[5] even if *N. gonorrhoeae* is negative. In addition, a recent report has clarified that it is feasible to use oropharyngeal specimens for the identification of *C. trachomatis* and *N. gonorrhoeae* by SDA.[6] Thus, if the PCR test was positive and the SDA test was negative, the result was defined as false-positive. The microbiological examination was performed at Mitsubishi Chemical Medience (Tokyo, Japan).

The protocol of this study was approved by the Institutional Review Board of Sapporo Medical University (17–45, 19-3050). Informed consent was obtained from all participants.

Seventy-nine male patients were included in this study. The median age was 28 years (range, 18 to 58 years). For the microbiological diagnosis, there were 41 patients (51.9%) with GU, including 4 with gonococcal and chlamydial urethritis; 11 (13.9%) with NGCU, and 27 (34.2%) with NGNCU.

Gonococcal detection in the pharynx with the SDA test was positive in 14 of the 79 patients with urethritis. The culture test was positive in 3 of these 14 patients with a positive SDA result. Of the 41 patients with gonococcal urethritis, 13 (31.7%) were positive for pharyngeal *N. gonorrhoeae* with the SDA test (Table 1). Two of the 13 patients were also positive by the culture method. A positive PCR test with a negative SDA or culture test was found in 10 of the 41 patients with gonococcal urethritis.

Of the 38 patients with NGCU or NGNCU, there was only 1 (2.6%) who was positive for pharyngeal *N. gonorrhoeae* detected with the SDA test or culture test.

Recent reports[2,7] have shown that female commercial sex workers frequently had chlamydial and/or gonococcal infection in the pharynx. Female pharyngeal *N. gonorrhoeae* may be transmitted to the urethra in heterosexual men.[8] In addition, a high prevalence of pharyngeal *N. gonorrhoeae* and *C. trachomatis* infection among men who have sex with men (MSM) was reported.[9,10] In Japan, orogenital sexual intercourse is considered to be usual sexual behavior between young heterosexual partners.[2] Therefore, it is possible that not only female commercial sex workers but also ordinary young women have pharyngeal *N. gonorrhoeae* and *C. trachomatis* infection. However, there have been few studies of the frequency of detection of pharyngeal gonorrhea and chlamydia in heterosexual men.

Table 1. True-positive and false-positive results for pharyngeal gonorrhea detection in patients with gonococcal urethritis

Test results	Number positive	(%)	Total
SDA (+), culture (+), and PCR (+)	2	4.9%	13 (31.7%)
SDA (+), culture (−), and PCR (+)	7	17.1%	
SDA (+), culture (−), and PCR (−)	4	9.8%	
SDA (−), culture (−), and PCR (+)	10	24.4%	

In the present study, pharyngeal *N. gonorrhoeae* was found in 31.7% of the heterosexual male patients with gonococcal urethritis, and in 2.6% of those with nongonococcal urethritis. The prevalence in our study was relatively high compared to those in other reports, which may reflect the different patient population. In our study, we examined patients with urethritis. Previous studies included patients or asymptomatic MSM with various conditions. Therefore, patients with GU may have a higher rate of pharyngeal *N. gonorrhoeae* than others.

A previous study reported that water oral-throat rinses had 82% sensitivity and 99.7% specificity for the detection of *N. gonorrhoeae*.[11] In vivo oral-throat rinses were found to be less sensitive than pharyngeal swabs for detecting *N. gonorrhoeae*; however, the sensitivity and specificity of oral-throat rinse specimens may be sufficient for the screening of high-risk individuals. In the study noted above,[11] the study participants thought that oral-throat rinses were acceptable, preferable, and feasible when compared with pharyngeal swabs. The authors speculated that dilution by the saline used may have been associated with the lower test sensitivity of oral-throat rinses. However, theoretically, oral-throat rinses retrieve pathogens from the whole oral cavity and pharynx. Therefore, oral-throat wash specimens are adequate to test with a nucleic acid amplification test and to detect pharyngeal gonorrhea and chlamydia clinically. The biggest advantages of the oral-throat rinses are that they are easy to use and comfortable for the patients to provide specimens. Unfortunately, we were not able to directly compare oral-throat wash specimens with pharyngeal swabs. Thus, such studies will be needed to establish a new standard detection test for pharyngeal gonorrhea and chlamydia.

In 9.8% of our patients with gonococcal detection in the pharynx, the SDA test was positive, but both the culture and the PCR test were negative. A recent report[6] showed that the SDA test and the transcription-mediated amplification (TMA) test were superior to culture and the PCR test for the detection of oropharyngeal *N. gonorrhoeae*. Therefore, our results may reflect the difference in sensitivity between the SDA test, culture, and PCR. However, further research will be needed to compare the sensitivity and specificity of these three nucleic acid amplification tests for the detection of *N. gonorrhoeae* in oropharyngeal specimens.

In conclusion, oral-throat wash with a nucleic acid amplification test can detect pharyngeal *N. gonorrhoeae* easily and efficiently. The prevalence of pharyngeal gonorrhea was clearly higher in patients with GU than in other male groups with NGCU or NGNCU.

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HPV 感染症－男性の無症候性感染－

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HPV 感染症－男性の無症候性感染－

Asymptomatic male HPV infection

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外陰部に腫瘤性病変を認めないような無症候性の男性における、外陰部の HPV 感染について、現状、問題点についてまとめた。無症候性 HPV 感染は、4.7%～43.0%の男性に認められると報告されており、少なくとも数カ月程度は持続する可能性が高い。性的パートナー間での HPV 感染の意義、包皮の状態（冠状切開の意義）については、HPV 感染との関連は、確立されておらず、議論のあるところである。今後は、男性での HPV 感染に関する疫学、感染持続期間の検討を進めるとともに、男性における無症候性 HPV 感染の意義を明らかにする必要がある。

We summarized the current epidemiological status of and issues concerning asymptomatic genital HPV infection in men. In previous studies, the detection rates of human papillomavirus (HPV) in the external genitalia of asymptomatic men varied from 4.7% to 43.0% and HPV could be detected for at least several months. The clinical relevance of HPV infection between sexual partners and the association between HPV infection and the prepuce or circumcision status remains a controversial issue. In the future, we need additional research on the epidemiology and longitudinal infectious status of male genital HPV infection to clarify the significance of asymptomatic male genital HPV infection.

Key words : human papillomavirus, asymptomatic healthy male

はじめに

性器における human papillomavirus（HPV）感染は、女性の子宮頸癌との関連から、その自然史を含めてきわめて多くの研究がなされてきた。しかし、男性では、尖圭コンジローマの罹患率もそれほど高いわけではなく、HPV との関連がある陰茎癌の罹患率も子宮頸癌と比較するときわめて低いことから、女性への HPV 感染ほど多くの研究がなされてきたわけではなかった。ただ、性感染症という見地から考えると、パートナーである男性に関する研究も、女性と同様になされるべきであろう。

われわれは以前より外陰部に明らかな腫瘤性病変を認めない男性における HPV DNA の検出率に関して調査を行ってきた[1)-3)]。男性の外陰部からの HPV DNA 検出に関して、性感染症以外の泌尿器科受診患者では 17.1%、尿道炎患者では 24.5%程度であり、女性の子宮頸管からも妊婦で 25.8%、Commercial Sex Worker（CSW）で 49.3%の頻度で検出された[2)]。したがって、女性は言うまでもなく、男性の外陰部からも確かに HPV が検出されることが明らかにされている。そこで、本稿では、われわれの最近の研究結果とともに男性の HPV 感染の現状と今後の研究の展望について述べる。また、外陰部からの HPV DNA の検出と、無症候性 HPV 感染が同義であるかどうかの判断は一定していないと考える。文献でも双方の言葉が使われているのが現状である。したがって、本稿では、これらを同義に扱うが、文献での表現方法を尊重して用いることにする。

男性における HPV 感染の意義

性器 HPV 感染症は、HPV の遺伝子型により異なる疾患を発症する。HPV の 6 型と 11 型は尖圭コンジローマに関連するとされている。男性の尖圭コンジローマの罹患率は、29.9（10 万人・年対罹患率）と報告[4)]されており、男女での罹患率はほぼ同じ程度である。子宮頸癌と比較すると頻度は著しく低いものの男性の陰茎癌にも HPV の 16 型と 18 型など oncogenic type が関連しているとされている[5),6)]。この oncogenic HPV と関連している子宮頸癌と陰茎癌の罹患率の違いについての詳細は、明らかになってはいない。さらに、HPV と肛門癌との関連も指摘されている[6)]。これら男性の外陰部に腫瘤性病変を形成する疾患以外にも、無症候性 HPV 感染の報告[7)-14)]がある。

Table 1 Asymptomatic male genital HPV infection

Object	Sample number	Detection method	Detection rate	reference
Healthy volunteer	279	Hybrid Capture	4.7% (13/279)	7,8
Patients with urethritis	130	Hybrid Capture	18.5% (24/130)	7
Voluntary Finnish Army conscripts	234	PCR	7.1% (12/168)	9
Patients attending the STD clinic	235	PCR	13.2% (31/235)	10
New conscripts	337	PCR	33.8% (114/337)	11
Healthy men	96	PCR	42.7% (41/96)	12

男性における無症候性 HPV 感染（Table 1）

われわれは、外陰部からの HPV DNA 検出を目的に、279 人の無症候性健康成人男性と 130 人の外陰部に腫瘤を認めない尿道炎患者について検討を行った[7,8]。279 人の無症候性健康成人男性では、13 例（4.7%）で HPV DNA が検出された。このうち、過去 3 カ月に性交頻度があった群を sexually active group とすると、6.5%（200 例中 13 例）で検出された。130 人の尿道炎患者では、24 例（18.5%）で HPV DNA が検出され、sexually active group では、19.4%（124 例中 24 例）で検出された。75 人の無症候性健康成人男性と 130 人の尿道炎患者との比較[7]では、性交頻度、性交パートナー数で有意差があり、包皮の状態では有意差がなかった。つまり、HPV の検出率には性的活動性が関連していると考えられた。また、多変量解析では、過去の性感染症の既往が関連因子として選択された。また、包皮の状態は HPV 検出に関して関連を認めなかった。

無症候性成人男性を対象として HPV DNA 検出を試みた研究は、いくつか報告されている。それらの報告から無症候性 HPV 感染の頻度は、7.1%～42.7%[9)-12)]であり比較的幅広い。検討した地域や対象により検出頻度は異なるものの、検出頻度が性的活動性に関連する点は、われわれの研究と同様である。フィンランドからの報告[9]では、432 人のフィンランド軍男性兵士を対象にして、外陰部所見と細胞診の検討、擦過細胞の polymerase chain reaction（PCR）法での HPV DNA 検出を行った。外陰部に異常所見を認めない 234 例中、PCR 法を行うに十分な検体を有した 168 例中 12 例で HPV DNA 陽性であった。多変量解析では、HPV 検出に関して、性的パートナー数が多いこと、過去の性感染症の既往、コンドームの不使用が有意な危険因子であったとしている。スウェーデンからの報告[10]では、HPV に関連する疾患と無関係に受診した 235 人の検討では、陰茎を擦過した検体を用いて PCR 法で HPV DNA の検出を試みたが、31 人（13.2%）で HPV DNA が陽性であった。デンマークからの報告[11]では、新しくデンマーク軍に入隊した男性兵士を対象とし、337 人中 114 人（33.8%）で PCR 法により HPV DNA 陽性であった。メキシコでの 1998 年の無症候性健康成人男性を対象とした検討[12]では、sexually active であった 96 人中、42.7%が PCR 法で陽性であった。

報告により、その頻度に違いはあるものの、男性の外陰部から、HPV DNA が検出されることは明らかである。決して低くはない頻度で無症候性の男性の外陰部に HPV が存在し、いくつかの研究では、その頻度は性的活動性に関係している[4,7]ことが指摘されている。

男性における無症候性 HPV 感染の自然史（HPV DNA 検出の持続期間）

女性においては、子宮頸部への持続的な無症候性 HPV 感染は、癌化との関連[16]が最も重要である。癌化とは無関係に自然史を検討した報告[16]では、2 年間で子宮頸部からの HPV DNA 検出率は 21%から 8.3%と低下し、同一型の検出は 3.4%（59 例中 2 例のみ）であった。また、長い場合でも平均 18ヵ月程度の検出期間であるとの報告[17]もある。

HPV DNA 検出を経時的に検査したわれわれの検討[7]では、無症候性健康成人男性の HPV 陽性 1 例のみで検討可能であったが、その 3ヵ月後にも陽性だったが、さらに 3ヵ月後には陰性化した。尿道炎患者の陽性例では、18 例で検討し、初診から再診までが中央値 11 日（3～30 日）で、再診時の陽性が 16 例、陰性化が 2 例であった。さらに、16 例の陽性症例では、14 例で再々診がなかったものの、残りの 2 例中、1 例は初診から再々診まで 35 日、もう 1 例は初診から再々診まで 145 日で、いずれも陽性であった。

デンマークの研究[11]では、6ヵ月前後の間隔で HPV DNA 検出を試みている。最初の検査で陽性であった 83 例のうち、6ヵ月後でも 60 例が陽性であり、23 例で陰転化していた。また、最初の検査で陰性であった 167 例では、6ヵ月後でも 144 例で陰性であり、23 例で陽転化していた。陽性が持続することの危険因子としては、多数の DNA 型が検出されることであった。最初の検査で陽性であった 73 例のうち、検討可能であった 42 例では同じ DNA 型が 6ヵ月後の検査でも検出された。

HPV DNA 検出の自然史の研究では、長期間の観察での再感染により持続的な検出となる危険を避けることができないが、われわれの研究と、このデンマークの研究から、数ヵ月単位で観察した場合には、HPV DNA は、持続的に検出される頻度が高いということがいえる。ただ、男性では、女性と比較して持続感染しづらいのではないかとの報告[18]もあり、さらに長期的に持続するかどうかは明らかではない。

性的パートナー間での検出

性的パートナー間での HPV 感染の意義は、STD という観点から考えると非常に重要である。HPV DNA 検出という目的で、性的パートナーを対象に検討した報告も散見される。コルポスコピー、もしくは細胞診で何らかの異常所見を指摘された女性とその性的パートナーについて検討した報告[19]によると、女性の子宮頸管から PCR 法により 89.9%（237 人中 213 人）で HPV DNA が検出され、男性の陰茎擦過検体から 72.9%（181 人中 132 人）で検出された。DNA 型別では、男女ともに 16 型がもっとも高頻度であり、それぞれ 59.4%、52.9%であった。さらに、検討可能であった対象では 116 組で両パートナーともに HPV 陽性であり、さらに、その中の 67 組（57.8%）で少なくとも一つの DNA 型が一致し、6 組（8.9%）で二つの型が、1 組（1.5%）で三つの型が一致した。両パートナー共通の型では、16 型が 62.7%と最も多く検出され、次いで、31 型（7.5%）、51 型（6.0%）であった。これらの結果から、HPV の感染は性的パートナー間で生じているという結論を述べている。同様の検討[20]では、STD クリニック受診の 45 組の性的パートナー間で PCR 法により HPV DNA を検出したところ、両パートナーともに陽性であったのが 20 組であり、このうち同一の DNA 型であったのが、13 組であった。この結果から、性的パートナー間での HPV 感染の意義を強調している。しかし、性的パートナー間での感染に対して否定的な報告[21]もある。Pap スメアの異常を指摘され婦人科を受診した女性とその性的パートナーの 270 組について、*in situ* hybridization、もしくは PCR 法で生検組織から HPV DNA の検出を試みた。両パートナーともに陽性であったのが、66 組であったが、同一の DNA 型は 15 組のみであり、性的パートナー間での HPV 感染の意義は低いのではないかとしている。

最新の詳細な検討[19]では、性的パートナー間での HPV 感染の意義を強調しており、すでに、予想していた点が裏づけられたと考えられる。しかし、性的パートナー間での経時的な感染の持続については、明らかではない。この点の解明が、性感染症という点からの HPV 感染の自然史研究をすすめるうえで重要であろう。興味深い研究結果[19]としては、男性から得られた陰茎擦過検体のウイルス量が女性の子宮頸管擦過検体よりも著明に少なかったことが、男女の HPV 感染の経過と関係しているかもしれない。

HPV 感染と環状切開（包皮の状態）の意義

HPV 感染と包皮の環状切開の有無との関連については、対立する意見が存在する[6]。環状切開が陰茎の HPV 感染の危険性を減少させるという報告[22]は、ブラジル、コロンビア、タイ、フィリピン、スペインの施設での研究をまとめたもので、陰茎、外尿道口、冠状溝を拭った綿棒を検体として PCR 法で HPV DNA を検出した。冠状切開未施行の男性では、HPV DNA 検出は 19.6%（847 例中 166 例）で、冠状切開後の男性では、5.5%（292 例中 16 例）で検出し、統計学的に有意差を認めた。同様に、冠状切開未施行の男性では HPV DNA の検出率が 44.0%であったが、冠状切開後の男性では HPV DNA は 29.5%で検出されたとの報告[13]もある。一方では、冠状切開未施行例と冠状切開後の男性で HPV DNA 検出率に差がないとの報告[14]もある。われわれの研究結果[7]も、HPV 感染と包皮の状態の関連については否定的なものであった。冠状切開後の男性はより衛生的であり、より高いレベルの教育を受けていたという記述[22]もあり、HPV 感染と包皮の状態の関連についての結論は得られていない。

まとめ

男性の HPV 感染に関する研究は、未だ十分とはいえないが、事実として、生命に影響を及ぼす疾患との関連でいえば、女性の HPV 感染がより重要であるといえる。しかし、性的パートナー間で感染を生じると考えるならば、男性の HPV 感染に関する、疫学、自然史の研究は進められるべきであるし、性的パートナー間での感染についても、さらに詳細な検討がなされるべきであろう。男性の HPV 感染は、女性に対しても無関係ではないからである。また、男性に特有な包皮の状態についても、HPV 感染の危険因子としての臨床的な印象はあるものの、確立されてはいない。

今、男性の無症候性 HPV 感染について明らかなことは、男性の外陰部からは、確かに HPV が、検出されることである。そして、その検出、つまり、無症候性感染が少なくとも数ヵ月程度は持続するということである。それ以上の期間ではどうなるのかは明らかではないし、性的パートナー間での感染の意義、包皮の状態（冠状切開の施行・未施行）についても今後更なる研究が必要である。

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Case Report

Chlamydial seminal vesiculitis without symptomatic urethritis and epididymitis

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Abstract We previously reported that seminal vesiculitis was associated with acute epididymitis, and that *Chlamydia trachomatis* was the major causative pathogen for infection of the seminal vesicle, suggesting that seminal vesiculitis was a discrete disease entity. In this paper, we report two patients with bacteriologically and cytologically proven seminal vesiculitis who had asymptomatic urethritis but not epididymitis. The clinical courses of these patients suggest that chlamydial seminal vesiculitis may be a cause of asymptomatic infection of the urethra or subsequent development of acute epididymitis.

Key words acute epididymitis, and seminal vesicles, *Chlamydia trachomatis*, seminal vesiculitis, urethritis.

Introduction

We previously reported that seminal vesiculitis was closely linked with acute chlamydial epididymitis, and that *Chlamydia trachomatis* was frequently isolated from the seminal vesicles.[1] Thus, we speculated that the microorganism induced the disease process from urethritis to acute epididymitis through seminal vesiculitis. In this report, we present two patients with bacteriologically and cytologically proven seminal vesiculitis who had asymptomatic urethritis but not epididymitis

We discuss the clinical implications of chlamydial seminal vesiculitis as a single disease entity, in which the disease is not associated with symptomatic urethritis or acute epididymitis.

Case report

Case 1

A 23-year-old heterosexual man visited one of our clinics complaining of hematospermia. He had no specific voiding symptoms, urethral discharge or history of antimicrobial treatment. His female sexual partner was diagnosed as having chlamydial cervicitis and had already received appropriate antimicrobial treatment. Physical examination revealed no remarkable abnormalities in his urethral meatus, penis, testis, epididymis or prostate. No urethral discharge was found. Microscopic examination revealed two to three white blood cells (WBC) per high power field (h.p.f.) in sediment of the first voided urine, and many WBC per h.p.f. in semen. Transrectal ultrasonography (TRUS) imaging revealed dilation and cystic change on the right-side seminal vesicle (Fig. 1). After obtaining written informed consent, we did transperineal puncture of the seminal vesicles under TRUS. A smear sample of fluid from the right seminal vesicle had many WBC, but that from the left had no inflammatory finding. *C. trachomatis* was detected using a commercially available nucleic acid amplification test kit in first-voided urine, semen, and right seminal vesicle fluid, but not in fluid from the left vesicle. After treatment with oral levofloxacin 100 mg three times daily for 2 weeks, hematospermia disappeared with no detection of *C. trachomatis* in either the first-voided urine or right seminal vesicle fluid.

Case 2

A 32-year-old heterosexual man visited us for consultation of dense semen which he had first noticed 3 weeks earlier. He had a chance to contract a sexually transmitted disease 4 weeks before the visit. At the time of his visit, he had some discomfort of the urethra on voiding and pain on ejaculation. Physical examination revealed no remarkable abnormal findings in the genitalia. No urethral discharge was identified. Microscopic examination revealed one to two WBC per h.p.f. in sediment of the first voided-urine and five to six WBC in the expressed prostatic secretion (EPS), and many WBC per h.p.f. in semen. TRUS imaging revealed dilation and cystic change in the seminal vesicle on the right side. Only cystic change was observed in the seminal vesicle on the left side. *C. trachomatis* was detected in first-voided urine, semen, EPS, and right seminal vesicle fluid. He was treated with clarithromycin 200 mg twice daily for 2 weeks. After treatment, the semen character became normal and *C. trachomatis* was not detected in the first-voided urine sample or semen.

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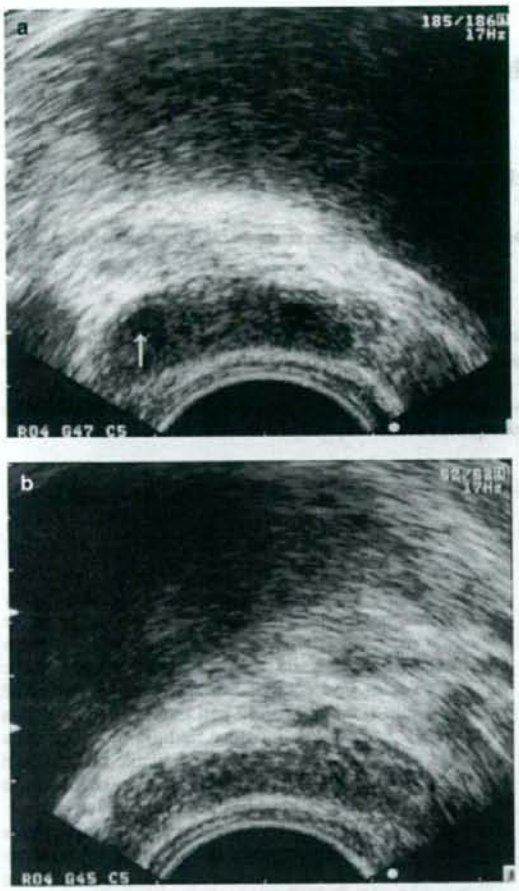

Fig. 1 Seminal vesicle images by transrectal ultrasonography (case 1). (a) The right-side seminal vesicle was enlarged and dilated with multicystic changes. Arrows indicate cystic changes. (b) The left-side seminal vesicle was not dilated.

Discussion

As we indicated in a previous study, chlamydial seminal vesiculitis is a distinct clinical entity.[1] Since the study demonstrated that most of the heterosexual younger patients who developed acute epididymitis simultaneously had chlamydial urethritis and seminal vesiculitis, we speculated that the infection in the seminal vesicle preceded development of acute chlamydial epididymitis in some patients. However, the issue remains to be determined.

The two current patients had isolated chlamydial seminal vesiculitis without any obvious clinical symptoms or signs of epididymitis, suggesting that the disease might occur before the development of epididymitis as Krishnan and his colleague speculated,[2] although it would be associated with epididymitis in the subsequent follow up unless they were treated with antimicrobials.

It is also an intriguing finding that these two patients seemed to be asymptomatic even when they were revealed to have a positive result for *C. trachomatis* in the first-voided urine. We recently reported that the detection rate of *C. trachomatis* in the first-voided urine was 4% in 200 young men who were otherwise healthy and had no genital organ-related symptoms. Thus, the rate of latent or unrecognized infection of *C. trachomatis* in men is almost the same as found in women.[3,4] Seminal vesiculitis caused by this organism may serve as a source of its latent infection. However, further studies will be needed to provide definitive evidence.

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ORIGINAL ARTICLE

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Detection of *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum* DNAs in urine from asymptomatic healthy young Japanese men

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Abstract The aim of this study was to estimate the detection rates of *Mycoplasma* and *Ureaplasma*, which are presumptive causes of sexually transmitted diseases (STDs), in young men in Sapporo, Japan. In addition, we examined the associations among *Chlamydia trachomatis*, *Mycoplasma*, and *Ureaplasma*. A survey of 100 asymptomatic healthy male volunteers was carried out. *C. trachomatis*, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum* in first-voided urine specimens were detected by polymerase chain reaction assay. Detection rates were 1% for *M. genitalium*, 4% for *M. hominis*, 12% for *U. urealyticum*, and 23% for *U. parvum*. *C. trachomatis* was detected in 6% of samples. No *M. hominis*, *U. urealyticum*, or *U. parvum* was detected simultaneously in any sample positive for *C. trachomatis*. The detection rate of urinary *M. genitalium* was extremely low, which is similar to previous reports from Japan. The detection rates of urethral *U. urealyticum* and *U. parvum* were significantly related to sexual activity. We need to determine whether these pathogens have a role in the sexual transmission of disease or just in colonization.

Key words Asymptomatic · Male · *Mycoplasma* · *Ureaplasma* · *Chlamydia* · Japan

Introduction

Recent sexually transmitted disease (STD) surveillance revealed a significantly high incidence of such diseases in young men and women.[1] In men, gonococcal urethritis is one of the major STDs, and nongonococcal urethritis caused by *Chlamydia trachomatis* and *Mycoplasma genitalium* are also common. Although *C. trachomatis* and *M. genitalium* have been established as common pathogens of nongonococcal urethritis, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum* have also been presumed to be potential pathogens for this condition. However, there have been few reports on the detection rates of urinary *Mycoplasma* and *Ureaplasma* in asymptomatic healthy men in Japan. The aim of this study was to determine the detection rates of those pathogens in asymptomatic healthy young men in Sapporo, Japan. In addition, we examined the associations among *C. trachomatis*, *Mycoplasma*, and *Ureaplasma*.

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Patients and methods

The study included 100 healthy male volunteers who were recruited from university students for 2 weeks by advertisements that explained the study design and its clinical relevance. They were asked to respond to a self-administered questionnaire for information about age, marital status, history of STDs, average frequency of sexual intercourse in the previous 3 months, and number of current sex partners. The average frequency of intercourse was categorized as 3–5 times per week, 1–2 times per week, 3–4 times per month, 1–2 times per month, less than once per month, or none.[2] We defined men with no sexual intercourse in the previous 3 months as sexually inactive, and those who had sexual intercourse in that period as sexually active.[3] In addition, the men were asked to confirm that they did not have any symptoms such as pain on miction or ejaculation. The protocol of this study was approved by the Ethical Committee of Sapporo Medical University. Both verbal and written informed consent were obtained from each subject.

M. genitalium, *M. hominis*, *U. urealyticum*, *U. parvum*, *C. trachomatis*, and *Neisseria gonorrhoeae* were all detected in first-voided urine. The detection of *M. genitalium*, *M. hominis*, *U. urealyticum*, and *U. parvum* was carried out with the special polymerase chain reaction (PCR) method reported by Yoshida et al.[4] These tests were done in a commercial laboratory (Mitsubishi Kagaku Bio-Clinical

Table 1. The backgrounds of the healthy male volunteers

Age (years)	Average 22.45 (±2.9)	Median 22 (18–35)
Marital status	Single	99
	Married	1
History of STD	Genital herpes	1
	Urethritis	3
Average frequencies of sexual intercourse	3–5 times/week	5
	1–2 times/week	24
	3–4 times/month	18
	1–2 times/month	16
	Less than once per month	12
	None	25
Number of current sexual partners	More than 3	6
	One	52
	None	42

Table 2. *C. trachomatis*, *Mycoplasma*, and *Ureaplasma* detected

Number	*Chlamydia trachomatis*	*Mycoplasma genitalium*	*Mycoplasma hominis*	*Ureaplasma urealyticum*	*Ureaplasma parvum*
5	+	−	−	−	−
1	+	+	−	−	−
1	−	−	+	+	+
2	−	−	+	−	+
1	−	−	+	+	−
2	−	−	−	+	+
18	−	−	−	−	+
8	−	−	−	+	−
62	−	−	−	−	−
Total 100	6	1	4	12	23

+, positive; −, negative

Table 3. Comparison between sexual activity and the detection of *Mycoplasma* and *Ureaplasma*

Average frequency of sexual intercourse	*Mycoplasma genitalium*	*Mycoplasma hominis*	*Ureaplasma urealyticum*	*Ureaplasma parvum*	Total
3–5 times/week	0	1 (25%)	3 (27%)	1 (4%)	5
1–2 times/week	0	1 (25%)	3 (27%)	8 (35%)	24
3–4 times/month	1 (100%)	1 (25%)	2 (18%)	6 (26%)	18
1–2 times/month	0	1 (25%)	2 (18%)	6 (26%)	16
Less than once per month	0	0	1 (9%)	1 (4%)	12
None	0	0	0	1 (4%)	25
Total	1	4	11	23	100

Laboratories, Tokyo). Detection of *C. trachomatis* and *N. gonorrhoeae* in first-voided urine was carried out with a commercially available PCR assay (Amplicor STD-I; Hoffmann-La Roche, Basel, Switzerland). Statistical analysis was done by the Kruskal–Wallis test.

Results

The backgrounds, including the sexual activity, of the healthy male volunteers are summarized in Table 1. One-quarter of the participants were sexually inactive. The detection rates of *M. genitalium*, *M. hominis*, *U. urealyticum*, and *U. parvum* were 1%, 4%, 12%, and 23%, respectively (Table 2). In the 75 sexually active men, the detection rates were summarized as *M. genitalium* in 1.3%, *M. hominis* in 5.3%, *U. urealyticum* in 16.0%, and *U. parvum* in 29.3% (Table 3). The detection rate of *U. urealyticum* was significantly correlated with the frequency of sexual intercourse ($P = 0.0072$). In addition, there was also a statistically significant difference between the detection rate of *U. parvum* and the frequency of sexual intercourse ($P = 0.0131$). There was no statistical difference between the rate of *M. hominis* and the frequency of sexual intercourse. Although *C. trachomatis* was detected in 6% of participants, *M. hominis*, *U. urealyticum*, and *U. parvum* DNAs were not detected in the samples which were positive for *C. trachomatis*. *N. gonorrhoeae* was not detected in any sample.

Discussion

Although *C. trachomatis* is the principal pathogen of nongonococcal urethritis (NGU), *M. genitalium* plays an important role in the development of male NGU.[5] However, it has been suggested that some strains of *Mycoplasma* and *Ureaplasma* are potentially associated with male urethritis. Yoshida et al.[4] established the phylogeny-based identification of PCR products, and detected *M. genitalium*, *M. hominis*, *U. urealyticum*, and *U. parvum* as pathogens of NGU. Indeed, *U. urealyticum* may also be involved.[6] However, there are not enough data to be completely sure that *U. urealyticum*, *U. parvum*, and *M. hominis* are actively involved in male NGU.

The detection rates of urinary *M. genitalium* were 1% in total, and 1.3% in asymptomatic sexually active men. Another report showed that 1.1% of asymptomatic Japanese men were positive for *M. genitalium*.[7] In reports from New Orleans and Denmark, 7% and 9%, respectively, of asymptomatic men were positive for *M. genitalium*.[8,9] The reasons for the differences in the data between Japan and other countries are not clear. One speculation was that the incidence of STDs was higher in New Orleans.[8] Recently, Falk et al.[10] reported that *M. genitalium* caused symptoms of urethritis among males with STD more often than *C. trachomatis*. This report suggested that *M. genitalium* could cause more active and more symptomatic male urethritis than *C. trachomatis*.

The detection rates of *U. urealyticum* and *U. parvum* were relatively higher than those of other STD pathogens in this study. In a study reported by Yoshida et al.,[4] the detection rates of *U. urealyticum* and *U. parvum* in the urine specimens of asymptomatic men were 9.5% (4 of 42) and 21.4% (9 of 42), respectively. Interestingly, the detection rate of *U. parvum* in the urine specimens of asymptomatic men was much higher than for patients with nongonococcal urethritis. Although we need additional data to determine whether *U. parvum* and *U. urealyticum* are definitive pathogens of urethritis, our data suggest that those pathogens might colonize in the urethra without any symptoms.

In addition, we examined the associations among *C. trachomatis*, *Mycoplasma*, and *Ureaplasma*. The results showed that positive *C. trachomatis* had no relationship to positive *M. hominis*, *U. urealyticum*, or *U. parvum*. Most positive samples were obtained from the volunteers in the sexually active group, and the positivities were presumed to be associated with sexual activity. The reason why these pathogens could not be detected simultaneously remains unclear. In a previous report,[4] 45.7% (21 of 46) of specimens from nongonococcal nonchlamydial urethritis cases were positive for *Mycoplasma* or *Ureaplasma*. In addition, 17.4% (8 of 46) of the specimens from these cases were positive for *U. urealyticum* and 6.5% (3 of 46) were positive for *U. parvum*. It is assumed that there is a different mechanism for *Mycoplasma* and *Ureaplasma* to attach to or colonize the urethra from that for *C. trachomatis*. At present, we do not know if those organisms are active pathogens for male urethritis because little is known about their pathogenicity.

We determined the detection rates of asymptomatic potential STDs in healthy male volunteers in Sapporo, Japan. They were 1.3% for *M. genitalium*, 5.3% for *M. hominis*, 16.0% for *U. urealyticum*, and 29.3% for *U. parvum* in asymptomatic sexually active men in this study. Our study showed that the detection rates of urinary *M. hominis*, *U. urealyticum*, and *U. parvum* in asymptomatic men were not negligible, although asymptomatic *M. genitalium* urethral infection was extremely uncommon. The detection rates of *U. urealyticum* and *U. parvum* were higher than those for the other pathogens, and our results suggested that their detection was associated with sexual activity. In the future, we need to clarify whether those pathogens simply colonize the urethra, and the role played in their transmission to the sexual partner in the pathogenicity of cervicitis.

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ORIGINAL ARTICLE

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Analysis of clinical manifestations of male patients with urethritis

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Abstract Almost all physicians involved in treating sexually transmitted infections recognize the specific clinical manifestations of patients with urethritis. However, in previous studies, the diagnosis of gonococcal urethritis was based on cultures or staining methods. In this study, we examined in detail the clinical manifestations of patients with urethritis diagnosed by the nucleic acid amplification test (NAAT). A total of 154 patients with male urethritis were included in the study. The NAAT could distinguish 64 patients with gonococcal urethritis, 45 patients with chlamydial urethritis, and 45 patients with nongonococcal and nonchlamydial urethritis. Forty-three (67.2%) patients with gonococcal urethritis had more severe symptoms, i.e., moderate or profuse urethral discharge, and cloudy or purulent discharge, than patients with chlamydial urethritis, nongonococcal and nonchlamydial urethritis. There were 39 (86.7%) patients in the chlamydial urethritis group with mild symptoms, clear discharge or none, and moderate or profuse discharge. Although the diagnosis of male urethritis can be performed by microbiological examination, the typical symptoms help us to distinguish each type of urethritis and understand this kind of disease.

Key words Male urethritis · Urethral discharge · Nucleic acid amplification test

Introduction

Male urethritis due to sexually transmitted infections (STIs) is generally classified as gonococcal urethritis (GU) or nongonococcal urethritis (NGU). Moreover, NGU is divided into chlamydial urethritis (CU) and nongonococcal and nonchlamydial urethritis (NGNCU). Almost all physicians involved in the treatment of STIs recognize that the urethral discharge of GU is generally purulent or cloudy, while that of NGU is clear.[1] However, in most reports, the diagnosis of GU was determined by culture or microscopic findings of Gram-negative diplococci. Therefore, some cases of GU might erroneously have been classified as NGU because the sensitivity of the culture method can be lower than that of the nucleic acid amplification test (NAAT).[2,3] From the point of view of the microbiological diagnosis of male urethritis, the NAAT is the most precise tool currently available because of its higher sensitivity and specificity. This means that, for the physician involved in the treatment and diagnosis of STIs, it is necessary to assess the various symptoms of male urethritis diagnosed by a NAAT in order to understand its pathology clearly. In other words, we should learn the symptoms of patients with male urethritis diagnosed by the NAAT, which has a high sensitivity and specificity for diagnosis. In this study, therefore, we analyzed in detail the symptoms of male patients with urethritis diagnosed by the NAAT.

Patients and methods

We analyzed the symptoms of male patients with urethritis who visited our clinics from January through July 2005. The definition of urethritis in this study included the symptoms of pain on miction, urethral discharge, urethral itching, and a reddish penile glans. We also included patients without apparent symptoms, but in whom *Neisseria gonorrhoeae* (*N. gonorrhoeae*) or *Chlamydia trachomatis* (*C. trachomatis*) had been detected. The microbiological diagnosis of ure-

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Table 1. The full findings of urethral discharges and the appearance of the penile glans

Findings	GU	CU	NGNCU
Quantitative findings[a]			
None	1 (1.6%)	25 (55.6%)	20 (44.4%)
Scanty	20 (31.3%)	18 (40.0%)	21 (46.7%)
Moderate	31 (48.4%)	1 (2.2%)	3 (6.7%)
Profuse	12 (18.8%)	1 (2.2%)	1 (2.2%)
Qualitative findings[b]			
None	1 (1.6%)	24 (53.3%)	19 (42.2%)
Clear	2 (3.1%)	16 (35.6%)	17 (37.8%)
Cloudy	22 (34.4%)	4 (8.9%)	6 (13.3%)
Pulurent	39 (60.9%)	1 (2.2%)	3 (6.7%)
Findings of the penile glans[c]			
None	13 (20.3%)	32 (71.1%)	21 (46.7%)
Mild	37 (57.8%)	12 (26.7%)	20 (44.4%)
Extreme	14 (21.9%)	1 (2.2%)	4 (8.9%)

[a] Scanty, discharge only on stripping the urethra; moderate, discharge at the external urethral meatus; profuse, discharge spontaneously dripping from the external urethral meatus
[b] Clear, mucoid, translucent, no discoloration; cloudy, opalescent, whitish; purulent, yellow to green
[c] None, no redness on the penile glans; mild, slightly reddish change on the penile glans; extreme, extremely reddish change on the penile glans
GU, gonococcal urethritis; CU, chlamydial urethritis; NGNCU, nongonococcal and non-chlamydial urethritis

thritis was determined using a commercially available NAAT (Amplicor STD-1; Roche Diagnostic Systems, Branchburg, NJ, USA), and the results were divided into GU, CU, and NGNCU groups. In the clinics, expert urologists looked over and recorded the full findings of urethral discharge[1] and the appearance of the penile glans (Table 1) in routine clinical examinations. The white blood cell (WBC) count in the sediment of first-voided urine was also documented. The WBC count was divided into 4 categories: 0 WBC per high power field (h.p.f.), 1–4 WBCs per h.p.f., 5–14 WBCs per h.p.f., and 15 or more WBCs per h.p.f. Interviews revealed the episodes which may have been responsible for the infection, and the main complaints which led to the visit to the clinic. The following reasons for infection were found: doing commercial sexual worker (CSW) with vaginal sexual intercourse or oral sexual intercourse, having a regular sexual partner, having a casual sexual partner, and unknown. We investigated the chief complaints of strong or mild pain on miction, and the desire for an examination for STIs because of positive STI pathogens in the sexual partner. Statistical analyses were done by the χ^2 test, and partly by Fisher's exact probability test.

Results

A total of 154 patients with male urethritis were included in this study. Their median age was 28 (16–52) years. The NAAT could identify 64 patients (41.5%) with GU, including 7 with both gonococcal and chlamydial urethritis, 45 (29.2%) with CU, and 45 (29.2%) with NGNCU. The full findings of the medical examinations are summarized in Table 1. Statistically significant differences ($P < 0.0001$) between GU and CU were found for the quantitative findings, the qualitative findings, and penile appearance. Similarly, significant differences between GU and NGNCU were found for the quantitative findings ($P < 0.0001$), the qualitative findings ($P < 0.0001$), and penile appearance ($P = 0.0087$). However, there were no significant differences in the quantitative and qualitative findings between CU and NGNCU, although there was a significant difference ($P = 0.0478$) in penile appearance. In addition, we compared the combined symptoms with scanty (quantitative) findings or none, and clear (qualitative) findings or none, as mild symptoms, with those with moderate or profuse (quantitative) findings, and cloudy or purulent (qualitative) findings, as serious symptoms. Of the patients with GU, there were 43 (67.2%) with serious symptoms and 3 (1.6%) with mild symptoms. Of the patients with CU, there were 39 (86.7%) with mild symptoms and just 1 with serious symptoms. Of the patients with NGNCU, 34 (75.5%) had mild symptoms and 2 (4.4%) had serious symptoms. The WBC count in the urinary sediment of patients with GU was higher than for those with CU or NGNCU (Table 2). There were significant differences in the WBC count between GU and CU ($P < 0.0001$), GU and NGNCU ($P < 0.0001$), and CU and NGNCU ($P = 0.0446$). In addition, there were significant differences between the WBC count and the quantitative findings ($P = 0.0009$), and the WBC count and the qualitative findings ($P = 0.0028$) in patients with GU. However, there were no significant differences in those factors in patients with CU and NGNCU. Only one GU patient, who was diagnosed despite atypical symptoms, complained of pain on miction. That patient had no urethral discharge, no abnormal penile appearance, and 1–4 WBCs per h.p.f. in his first-voided urine. There were 5 CU patients who were diagnosed in spite of atypical symptoms. Five patients had moderate or profuse, and cloudy or purulent, urethral discharge. In addition, 4 of these 5 patients had a reddish change to the penile glans. The opportunities for infection and the chief complaints are summarized in Table 3. The probable cause

Table 2. Distribution of the white blood cell (WBC) count in the urinary sediment of patients with urethritis

WBC count	GU	CU	NGNCU
0 WBC per h.p.f.	0	2 (4.4%)	1 (2.2%)
1–4 WBCs per h.p.f.	5 (7.8%)	9 (20.0%)	21 (46.7%)
5–14 WBCs per h.p.f.	5 (7.8%)	15 (33.3%)	13 (28.9%)
15 or more WBCs per h.p.f.	54 (84.4%)	19 (42.2%)	10 (22.2%)

h.p.f., high power field

Table 3. Opportunities for infection and chief complaints

	GU	CU	NGNCU
Opportunity for infection			
Commercial sexual worker	28[a] (43.8%)	5[b] (11.1%)	16[c] (35.6%)
Regular sexual partner	15 (23.4%)	32 (71.1%)	20 (44.4%)
Casual sexual partner	13 (20.3%)	5 (11.1%)	6 (13.3%)
Unknown	8 (12.5%)	3 (6.7%)	3 (6.7%)
Chief complaints			
Pain on miction (strong)	46 (72.0%)	4 (8.9%)	5 (11.1%)
Pain on miction (mild)	16 (25.0%)	25 (55.6%)	33 (73.3%)
STI examination	0	12 (26.7%)	4 (8.9%)

[a] Three by vaginal sex, 24 by oral sex, and 1 by both vaginal and oral sex
[b] Four by oral sex and 1 unknown
[c] One by vaginal sex, 12 by oral sex, 2 by both vaginal and oral sex, and 1 unknown

of infection with GU was mostly CSW, but that of CU was mostly the sexual partner. In addition, most GU patients were infected by oral sex. The causes of infection with NGNCU were both CSW and the sexual partner. There were significant differences between the chances of infection with GU and CU ($P < 0.0001$), and those for CU and NGNCU ($P = 0.0348$); however, there was no significant difference between those for GU and NGNCU ($P = 0.1272$). In the analysis of symptoms, strong pain on miction was found predominantly in patients with GU, and mild pain was predominant in patients with CU ($P < 0.0001$).

Discussion

Male urethritis is generally diagnosed based on urinalysis, microbiological examination, and symptoms. In adolescents and younger age groups, male urethritis is divided into GU, CU, and NGNCU based on the results of a microbiological examination. Almost all physicians working in STI clinics recognize that patients with GU have moderate or profuse, and cloudy or purulent, urethral discharge, and a reddish change to the penile glans, whereas it is generally supposed that NGU, including CU and NGNCU, patients have scanty and clear urethral discharge. Rothenberg and Judson[1] reported that 96% of 1795 GU patients diagnosed by culture had cloudy or purulent urethral discharge. Interestingly, in that study, 33% of 3594 NGU patients had clear urethral discharge, and 56% of them had cloudy or purulent urethral discharge. We agree with the diagnosis of GU in that report because we always encounter cloudy or purulent urethral discharge in that situation. However, we do not agree with the diagnosis of NGU because we usually see clear urethral discharge in NGU patients. In that situation, the diagnosis of GU must be correct because *N. gonorrhoeae* can be isolated by culture. However, some cases of GU might mistakenly be classified as NGU because the sensitivity of the culture method could be lower than that of the NAAT.[2,3] Therefore, we studied each symptom in patients with GU, CU, and NGNCU which was diagnosed based on the NAAT. Indeed, it is known that urethral discharges are usually profuse and purulent in men with GU, but are generally scant and mucoid in men with NGU.[4] In this study, we confirmed that the symptoms of patients with GU were more severe, in terms of the quantity and quality of the urethral discharge and the penile appearance, than those of patients with CU and NGNCU. There was only 1 patient with atypical symptoms, no urethral discharge, and no abnormal penile appearance in the GU group. Thus, we can diagnose GU by interpreting the typical symptoms of moderate or profuse, cloudy or purulent, urethral discharge and a reddish change in the penile glans, although microbiological diagnosis with the NAAT could be important. However, we should employ the NAAT for both *N. gonorrhoeae* and *C. trachomatis* owing to the high frequency of concurrent chlamydial infection. Our results showed that 11.0% of patients with GU had concurrent chlamydial infection.

The symptoms of patients with CU differed from those of patients with GU. In this study, 95.6% of patients with CU had only scanty urethral discharge or none, and 88.9% had clear urethral discharge or none. In addition, 71.1% of patients with CU had no abnormality in the appearance of the penile glans. In general, infections caused by *C. trachomatis* are more often characterized by no symptoms or by milder symptoms than is the case for gonococcal infections.[5] Thus, our results are in accord with the general data. However, the symptoms of patients with NGNCU

were similar in terms of the quantitative and qualitative findings of urethral discharge, but the reddish change in the penile glans in these patients was more frequent than in those with CU. There were no significant differences in the severity of symptoms between the patients with CU and NGNCU, although the symptoms of patients with NGNCU were slightly worse. *Mycoplasma genitalium* is the established pathogen of NGNCU, and the prevalence of *M. genitalium*-positive NGNCU cases is from 18.4% to 45.5% of all NGNCU patients.[6] *M. genitalium*-positive men had symptomatic urethritis more often than those infected with *C. trachomatis*.[7] Although asymptomatic *M. genitalium* infection in the urethra is less prevalent than asymptomatic *C. trachomatis* infection, clinical manifestations of NGNCU can be confused with those of CU.

First-voided urine sediment analyses showed that patients with GU had higher WBC counts than those with CU and NGNCU. Interestingly, patients with NGNCU had lower WBC counts than those with CU. We could confirm that there were few patients with GU who had no pyuria or a very low WBC count, and such findings could overturn the diagnosis of GU. On the other hand, discriminating between CU and NGNCU based on urinary findings was quite difficult. The opportunities for infection were very different between GU and CU. The circumstances of GU infection were mostly CSW and oral sex. Those of CU infection were mostly from the sexual partner. In Japan, it has been pointed out that *N. gonorrhoeae* is detected in pharyngeal specimens,[8] and pharyngeal *N. gonorrhoeae* may be infectious for urethritis. With recent changes in sexual behavior, this new transmission route can be a problem in diagnosis and treatment. As the chief complaint leading to a visit to a clinic, patients with GU had relatively stronger pain than those with CU or NGNCU. Unfortunately, we could not use a pain scale to obtain objective results. However, we confirmed that all patients with GU visited the clinic with pain on miction as their chief complaint. Most patients with CU or NGNCU had mild pain on miction, and some visited the clinic with no apparent symptoms.

In conclusion, we assessed the clinical manifestations of patients with GU, CU, or NGNCU. Patients with GU had more serious symptoms with regard to urethral discharge and penile appearance than those with CU or NGNCU. Although the diagnosis of male urethritis can be performed by microbiological examination, the typical symptoms help us to distinguish each type of urethritis. When we investigated urethritis by the NAAT, we could diagnose each type correctly. Thus, our results should help physicians to understand and diagnose these diseases.

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