

# When should adenoviral non-gonococcal urethritis be suspected? Two case reports

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## SUMMARY

The impact of Adenovirus as agent of non-gonococcal urethritis (NGU) is still poorly documented in the literature. We describe two cases showing that adenoviral infection should be reasonably hypothesized in men with dysuria and scant urethral discharge in addition to meatus inflammation and/or edema (meatitis) or conjunctivitis.

**Case 1:** a 55-year-old man came to our observation in July 2012 referring a 5-day-history of intense dysuria and scant mucoid urethral discharge. Physical examination revealed the urethral discharge referred, but also modest meatitis and an intense conjunctival hyperemia on his right eye. Adenoviral infection was investigated and Adenovirus DNA (type 37) was detected in both the urethral and conjunctival swabs.

**Case 2:** a 43-year-old man with intense dysuria, started 4-5 days earlier, came to our attention with his wife in August 2012. Scant urethral mucoid secretions, severe meatal inflammation of the male patient were revealed during physical examination. His wife instead complained of a 2-day history of intense burning eyes. Adenoviral infection was investigated and Adenovirus DNA (type 37) was positive both in the male urethral swab and in his wife's conjunctival swab.

Adenovirus seems to cause a distinct and recognisable clinical syndrome in men presenting with urethritis. Studies on the prevalence and role of Adenovirus as a causative agent of urethritis are limited. Moreover, as rapid advanced molecular microbiology is now available, we believe that extending the search to Adenovirus in sexually active men with dysuria, scant discharge in addition to meatitis or conjunctivitis, should be a useful approach improving our understanding about adenoviral NGU, and especially avoiding or stopping unnecessary empirical antibiotic therapy.

**KEY WORDS:** Non-gonococcal urethritis, Adenoviral urethritis, Adenoviral conjunctivitis.

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## INTRODUCTION

Adenoviruses were first cultured and reported as distinct viral agents in 1953. The *Adenoviruses* constitute the *Adenoviridae* family of viruses, which is divided into two genera, *Mastadenovirus* and *Aviadenovirus*. Human Adenovirus belongs to *Mastadenovirus* and there are six species (formerly called subgenera) called human Adenovirus A to F, and sub-species B1 and B2. A probable species G comprising adenovirus

type 52 has recently been described (Jones *et al.*, 2007).

Adenovirus infections occur worldwide in humans and the transmission of infection and disease varies from sporadic to epidemic. The most characteristic manifestation of this infection is conjunctivitis as part of the keratoconjunctivitis syndrome. In 1977, Adenoviruses were first reported in men with urethritis in Perth, Australia, during and after an outbreak of adenoviral eye infection (Harnett *et al.*, 1981). Despite this, the impact of Adenovirus as agent of non-gonococcal urethritis (NGU) is still poorly documented in the literature. It is difficult to determine if the most probable reason Adenovirus is unreported is that it is usually not considered, or if it is usually not considered because there is no evidence to suggest it is common.

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This manuscript describes two cases of non-gonococcal urethritis (NGU). Few cases of adenovirus-related NGU have been reported to date and the importance of this pathogen as an etiological agent of urethritis is probably underestimated. Interestingly the two diagnoses, made over the course of two months, were unrelated. This finding strongly supports a higher prevalence of adenoviral urethritis among the population.

## CASE REPORTS

### Case 1

A 55-year-old man came to our observation in July 2012 with a 5-day history of intense dysuria and scant mucoid urethral discharge for about 2 days. Physical examination revealed the urethral discharge referred, mild erythema of his urethral meatus (meatitis) and an intense conjunctival hyperemia in his right eye, so the patient was asked about the onset of conjunctival symptoms too. He confirmed intense burning in the right eye occurred simultaneously with urethral symptoms. He was married, sexually active, had no history of sexually transmitted infections and he was not on medication, included of antibiotics and antiviral drugs. The physical examination was negative for inguinal lymphadenopathy or ulcers.

Copan Liquid Amies Elution Swab (Brescia, Italy) was used to collect and transport urethral samples for solid culturing of common bacteria and *Neisseria gonorrhoeae* according to laboratory-defined standard procedures. *Trichomonas vaginalis* was cultured in broth (Vagicult, Orion Diagnostica), while culture of urogenital mycoplasmas (*Mycoplasma hominis*, *Ureaplasma urealyticum/parvum*) was performed by Mycoplasma IST 2 kit (Biomerieux, Mercy l'Etoile, France).

Copan's flocculated swab and UTM viral transport were used to collect and transport urethral and conjunctival samples for molecular investigations. In particular, *Chlamydia trachomatis* was tested by COBAS TaqMan CT Test (Roche Molecular Diagnostics Tests) while HSV 1-2 and Adenovirus by commercial real time PCR (PCR Alert Kit Elitech, Nanogen Advanced Diagnostics and EuSepScreen, Eurospital, respectively;

Applied Biosystems 7300 Real Time PCR System).

Copan Liquid Amies Elution Swab, and UTM viral transport media were also used for conjunctival samples. Other than common bacteria, *Chlamydia trachomatis*, HSV-1, HSV-2, and Adenovirus, in conjunctival swabs *Enterovirus* and *Varicella-zoster virus* (PCR Alert Kit Elitech, Nanogen) were also investigated.

Gram-stained urethral-swabbed smear showed 1-4 polymorphonuclear leucocytes (PMNLs) per high power field (HPF) (x 1000 magnification).

Of all microorganisms investigated, only Adenovirus DNA was detected either in urethral and conjunctival-swabbed samples. Typing was performed for both positive samples and was positive for Adenovirus type 37. The patient went into spontaneous resolution of symptoms in about 1 week.

### Case 2

A 43-year-old man with intense dysuria, started 4-5 days before, came to our attention with his wife in August 2012. Scant urethral mucoid secretions, severe erythema and edema of the external urethral meatus of the male patient, but neither ulcers nor lymphadenopathy, were revealed during physical examination. His wife instead complained of a 2-day history of an intense burning eyes.

Neither patient had a history of sexually transmitted infections and they were not on medication, included of antibiotics and antiviral drugs. We asked the male patient about his sexual practices in the last few days and, in the light of Case 1 experienced a few days before, if he also had ocular symptoms in the last few days. He confirmed oral sex practices with his wife 3-4 days before the onset of symptoms, but denied any trouble to his eyes. Urethral swab and conjunctival swab were collected from the man and his wife respectively. Microbiological investigations were performed as described for Case 1.

Gram-stained urethral-swabbed smear showed 4-5 PMNLc/HPF. Of all microorganisms investigated (see Case 1) only search for Adenovirus DNA was positive both in urethral swab of the patient and in conjunctival swab of his wife. Typing was performed for both positive sam-

ples and was positive for Adenovirus type 37. As in Case 1, patient 2 also went into spontaneous resolution of symptoms in about 10 days.

## DISCUSSION

Acute NGU is one of the most common conditions in men attending sexually transmitted disease departments yet despite considerable research efforts the etiology of up to 50% of cases remains unknown. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the primary pathogens identified in men with urethritis (Centers of Disease Control, 2011). *Mycoplasma genitalium* is a common cause of NGU, while *Mycoplasma hominis* and *Ureaplasma species* are common in men with urethral symptoms, but their exact role as a pathogen has not been clearly defined (Moi *et al.*, 2009). *Trichomonas species* may also cause urethral symptoms in men but is difficult to detect (Schwebke *et al.*, 2003). Only two viruses have been implicated as cause of male urethritis, HSV (1-2) and Adenovirus (Bradshaw *et al.*, 2006).

There are few reports in the literature of Adenovirus-associated urethritis in men, probably because it is still wrongly considered an uncommon cause of urethritis in males. An excellent clinical study of the etiology of NGU (Bradshaw *et al.*, 2002) provides strong support for the addition of Adenovirus to the list of urethral pathogens in men. Adenoviruses, in particular types 8 and 37 (Subgenus D), seem to cause a distinct and recognisable clinical syndrome in men presenting with urethritis (Bradshaw *et al.*, 2006; Bradshaw *et al.*, 2002; Tabrizi *et al.*, 2007; Harnett *et al.*, 1984). Studies on the prevalence and role of Adenovirus as a causative agent of urethritis are limited. A recent report from Japan also describes a case of Adenovirus type 56 urethritis and conjunctivitis and proposes the role of Adenovirus as a possible sexually transmitted pathogen (Hiroi *et al.*, 2012).

Adenovirus has also been shown to infect the female genital tract and has been isolated in women with labial ulcers, vulvo-vaginitis, and cervicitis (De Jong *et al.*, 1981; Swenson *et al.*, 1995; Stanescu *et al.*, 1989; Pisani *et al.*, 1999). Sexual transmission appears to be the most plausible mode of acquisition of urethral infec-

tion, either through oral or possibly vaginal sex. Conjunctivitis may occur through autoinoculation or be related to sexual activity. Moreover, adenoviral conjunctivitis is highly contagious and it is not surprising that other family members rapidly become infected (O'Mahony, 2006). Despite this, evidence that Adenovirus-associated NGU is sexually transmitted is incomplete at this point. It is difficult to determine if the most probable reason Adenovirus is unreported is that it is usually not considered, or if it is usually not considered because there is no evidence to suggest it is common.

Clinically, urethritis caused by Adenovirus is characterised by severe dysuria, more than that usually reported by men with bacterial urethritis. Despite the intense dysuria, discharge is scant, and meatitis could be present. Most men with adenoviral urethritis also present meatitis, which is seen in a minority of cases caused by bacteria (Bradshaw *et al.*, 2006; Bradshaw *et al.*, 2002; O'Mahony, 2006; Martin, 2008; Azariah and Reid, 2000; Tabrizi *et al.*, 2007). Adenoviral urethritis is self-limited and usually does not require treatment. Effective antiadenoviral drugs are not available. The spontaneous resolution of the infection could prevent patients from reporting the disease to physicians leading to an underestimation of the number of cases. Neither patient examined had been treated either before or after sample collection. Their physician's suggestion, in both cases, was to wait for laboratory results, available after 3 days, and to start antibiotics only in case of worsening symptoms. Both went into spontaneous resolution in 7-10 days.

Adenovirus cases tend to occur in the fall and winter and are often associated with conjunctivitis (Bradshaw *et al.*, 2006). Surprisingly, contrary to other reports (Bradshaw *et al.*, 2002; O'Mahony, 2006), we describe two cases clustered between July and August 2012, the summer season in Italy, which does not correspond to the respiratory virus season. However, in both our cases we found a concordance in clinical features and the microscopic picture described in the literature (Bradshaw *et al.*, 2006; Bradshaw *et al.*, 2002). In both cases, the reported Gram-stained urethral-swabbed smear showed 1-5 range of PMNLs/HPF. Previous studies have reported that a significant proportion of men

with NGU and urethral pathogens have <5 PMNLs/HPF (Bradshaw *et al.*, 2006).

Dysuria, scant discharge, meatitis and/or conjunctivitis, remission of symptoms without empirical antibiotic or antiviral therapy within 7-10 days, detection of Adenovirus DNA in urethral specimens and negativity to all others microorganisms investigated, all support Adenovirus as a cause of urethritis in both cases described. DNA templates from urethral and conjunctival samples of Case 1 and the urethral sample of Case 2, stored at -20°C, were also re-evaluated for *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma genitalium*, *Mycoplasma hominis* and *Chlamydia trachomatis* by multiplex real time PCR (Anyplex™ II STI-7, Seegene, Korea). All negative results were confirmed, and *Mycoplasma genitalium* DNA was not detected.

In conclusion, when should adenoviral nongonococcal urethritis be suspected? We have reported two cases showing that adenoviral infection should be reasonably hypothesized in men with dysuria and scant urethral discharge in addition to meatus inflammation and/or edema (meatitis) or conjunctivitis, or recent sexual contact with partners with signs of acute upper respiratory infections. As rapid advanced molecular microbiology is now applied to the study of sexually transmitted infections (Martin, 2008), we suggest considering Adenovirus in all cases of dysuria, scant discharge in addition to meatitis and/or conjunctivitis in sexually active men. This should be a useful and reasonable diagnostic approach improving our understanding of the real prevalence of adenoviral NGU, and, especially, cautiously avoiding or promptly stopping unnecessary empirical antibiotic therapy.

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