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CASE REPORT

Epididymitis Caused by Coxsackievirus A6 in Association with Hand, Foot, and Mouth Disease

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Coxsackievirus A6 (CV-A6) caused hand, foot, and mouth disease (HFMD) with a unique manifestation of epididymitis. The patient underwent operation due to suspicion of testicular torsion. Epididymitis was diagnosed by ultrasound examination. Enterovirus was detected from epididymal fluid by PCR and typed by partial sequencing of viral protein 1 as CV-A6.

CASE REPORT

The case patient was a 17-year-old male who had previously been in good health. He was not on any regular medication. He sought medical care at the emergency department of the Oulu University Hospital due to an intense pain in his left testis. He was admitted to the surgical ward with suspicion of a testicular torsion. On admission, his general condition was good. He had mild fever and swelling in the left side of the scrotum, and that area was painful in palpation. Vesicular exanthema had appeared on his palms during the week before admission to the hospital.

Due to the suspicion of testicular torsion, an ultrasound examination was performed, which revealed epididymo-orchitis. The right testicle was normal when examined by ultrasound. Because the possibility of torsion could not be excluded, an exploratory operation was performed. The left testis and epididymis were found to be swollen and irritated. There was no pus in the scrotal area, but under the tunica vaginalis there was a small amount of fluid, which was aspirated and sent for the microbiological analysis. Antimicrobial treatment was started with cefuroxime and ciprofloxacin. After the operation, the patient remained on the ward for 3 days, and on discharge, he was recovering; he was afebrile and did not have any pain or swollenness in the scrotal area.

Laboratory analysis showed an increased blood C-reactive protein (CRP) level of 105 mg/ml (normal level, <10 mg/liter). On discharge, the CRP level was 30 mg/ml. The white blood cell count was normal (6.2 to 7.8 $\times$ 10^9/liter). A bacterial culture from the epididymal fluid gave a negative result, as did a urine culture. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* PCR test results from epididymal fluid were negative.

The patient had mild fever and small vesicles on palms before the admission to the hospital, which led the clinician to suspect a viral etiology. Therefore, enterovirus PCR was performed from the epididymal-fluid sample. An in-house reverse transcriptase PCR (RT-PCR) with primers derived from the 5′ noncoding region of enterovirus genome was performed (1). The PCR test gave a positive result. Because CV-A6 had been circulating in Finland and causing hand, foot, and mouth disease (HFMD), PCR with CV-A6-specific primers (1) was also performed and gave a positive result. For typing the enterovirus, RT-PCR with primers specific for a partial sequence of viral protein 1 was performed (2). The amplicons were sequenced and processed in a BLAST search, confirming that the sequence corresponded to CV-A6 (http://www.ncbi.nlm.nih.gov/nucleotide; see below for the GenBank accession number). The level of enterovirus IgG antibodies from the sera was slightly elevated at 82 enzyme immunoassay units (EIU; the cutoff value for a positive enterovirus IgG result is 10 EIU), and enterovirus IgM antibodies were also detected, confirming a recent enteroviral infection.

Coxsackievirus A6 (CV-A6) is a member of human enterovirus species A in the genus *Enterovirus* in the family of Picornaviridae. The most common clinical manifestation of CV-A6 infection is herpangina, a febrile illness with vesicular lesions on oral mucosa mainly affecting children. Other clinical manifestations include central nervous system infections.

In 2008, the virus emerged as a cause of HFMD (3), which is a childhood febrile illness manifesting with vesicular exanthema on hands, feet, and oral mucosa caused mainly by coxsackievirus A 16 and enterovirus 71. Since then, CV-A6 has been associated with global HFMD outbreaks. The features of CV-A6 HFMD have been atypical and more severe than those seen in manifestations of the classic disease, and adults have also been affected (3–6).

In a large CV-A6 outbreak in Singapore and in France, patients mainly had herpangina (7, 8), whereas CV-A6 infections in an outbreak in Taiwan occurred as macular or vesicular lesions on palms, soles, and oral mucosa (9). Atypical HFMD presenting with onychomadesis (nail shedding) caused by CV-A6 was first reported from Finland and Spain (3, 10). Unusual lesions on the scalp (11) and perioral and perirectal papules, as well as vesicles on the dorsum of the hands (12), have been shown. Recently, atypical HFMD cases with exsanthema resembling chickenpox or eczema herpeticum were reported from the United Kingdom (4).

The patient presented in this paper had a unique manifestation of CV-A6 infection as an epididymitis. On admission, the patient gave a history of previous febrile illness with vesicular rash on

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palms and soles, and his sister had same symptoms, which suggested a contagious disease as an etiology. Within the previous 3 months, there were also two other young males with similar testicular symptoms who were subjected to exploratory operations performed by the same urological team due to suspicion of testis torsion. However, the suspicion could not be confirmed in the operation. Atypical clinical features as well as the admission of and an operation performed on the third patient within a quite short period of time led to the suspicion of a contagious viral disease. Vesicular exsanthema on palms suggested enterovirus as a possible etiologic agent. Because infection was not suspected in the first two surgical cases, no samples for microbiological detection were taken; thus, a possible common source of exposure for the cases could not be confirmed. However, anamnesis showed that, before the admission to the hospital, the patients had had symptoms of a viral infection, such as mild fever. Thus, this implies that epididymitis of viral origin might have been more common than was suspected. Several enterovirus types circulate during epidemics; therefore, we cannot speculate about the virus-specific tropism of CV-A6 with respect to epididymal tissue on the basis of a single case.

Bacteria are the most common cause of epididymitis in adults, while orchitis (sometimes associated with mumps) is the classic complication of viral infection (13). A bacterial etiology is defined in 64% of the cases, and the bacteria cause infections in young men under 35 years as commonly as in older men (14). Epididymitis in boys under 14 years is considered to be mainly a postinfection inflammatory process (15).

The outcome of epididymitis is usually self-limiting and favorable, but mumps orchitis may lead to testis atrophy and an increase in the likelihood of infertility (13). Significant changes in sperm protein composition have recently been found to occur following epididymitis (16).

This is the first report to show that enteroviruses can be detected from epididymal fluid, indicating virus replication in the tissue. Epididymitis in young boys has been thought to be a postinfection inflammatory phenomenon on the basis of the finding that the patients had symptoms of upper respiratory infections preceding scrotal symptoms (15). Viruses have also been detected in nasopharyngeal specimens or stool samples, and patients have had higher virus antibody levels in sera than controls (15).

The patient described here underwent a first surgery due to suspicion of testicular torsion. However, the final diagnosis was epididymitis caused by an enterovirus. Clinical caution is important to recognize unusual clinical presentations of HFMD and an atypical etiology of epididymitis in order to avoid unnecessary invasive procedures as well as inappropriate antibiotic treatments. Our experience suggests that viral epididymitis should be suspected in young men with a recent history of HFMD who present with testicular pain.

Nucleotide sequence accession number. The sequences determined in this work were deposited in GenBank (http://www.ncbi.nlm.nih.gov/nucleotide) under accession number KF687973.

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