

1 **Epididymitis caused by coxsackievirus A6 in association of hand, foot and**
2 **mouth disease**

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30 **Abstract**

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34 Coxsackievirus A6 (CV-A6) caused hand, foot and mouth disease (HFMD) with unique

35 manifestation of epididymitis. The patient underwent operation due to suspicion of testicular

36 torsion. Epididymitis was diagnosed by ultrasound examination. Enterovirus was detected from

37 epididymal fluid by PCR and typed by partial sequencing of viral protein 1 as CV-A6.

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39 **CASE REPORT**

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41 The case patient was 17 y.o. male, who was previously in good health. He was not on any regular
42 medication. He sought medical care at the emergency department of the university hospital due to
43 an intense pain in his left testis. He was admitted to the surgical ward as a suspicion of a testicular
44 torsion. On admission his general condition was good. He had mild fever, swelling in the left side
45 of scrotum and this area was painful in palpation. Vesicular exanthema had appeared on palms
46 during the week before admission to hospital.

47

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

56

57 Laboratory analysis showed increased blood C-reactive protein level 105 mg/ml (normal level
58 < 10mg/l). On discharge CRP was 30 mg/ml. White blood cell count was normal ($6.2-7.8 \times 10^9/l$).
59 Bacterial culture from the epididymal fluid was negative, as well as was urine culture. *Chlamydia*
60 *trachomatis* and *Neisseria gonorrhoea* PCR tests from epididymal fluid were negative.

61

62 The patient had mild fever and small vesicles on palms before the admission to the hospital, which
63 led the clinician to suspect a viral etiology. Therefore enterovirus PCR was performed from

64 epididymal fluid sample. An in-house RT -PCR with primers derived from the 5' -non-coding
65 region of enterovirus genome was used (1). The PCR test gave a positive result. Because CV-A6
66 had been circulating in Finland causing HFMD, also PCR with CV-A6 specific primers (1) was run,
67 which was positive. For typing the enterovirus, RT -PCR with primers specific for a partial
68 sequence of viral protein 1 was performed (2). The amplicons were sequenced and run in the
69 BLAST search confirming the sequence as CV-A6 (<http://www.ncbi.nlm.nih.gov/nucleotide>,
70 GenBank accession number: KF 687973) Enterovirus IgG antibodies from the sera were slightly
71 elevated, 82 EIU (enzyme immunoassay units; cut-off value for positive enterovirus IgG is 10 EIU),
72 and also enterovirus IgM antibodies were detected confirming a recent enteroviral infection.

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

80

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

86

87 In a large CV-A6 outbreak in Singapore and in France patients mainly had herpangina (7,8),
88 whereas in an outbreak in Taiwan CVA6 infections occurred as macular or vesicular lesion on

89 palms, soles and oral mucosa (9). Atypical HFMD presenting with onychomadesis, nail shedding,
90 caused by CV-A6 was first reported from Finland and Spain (3,10). Unusual lesions on scalp (11)
91 and perioral and perirectal papules, as well as vesicles on the dorsum of the hands (12) have been
92 shown. Recently, atypical HFMD cases with exanthema resembling chickenpox or eczema
93 herpeticum was reported from United Kingdom (4).

94

95 The patient presented in this paper had a unique manifestation of CV-A6 infection as an
96 epididymitis. On admission the patient gave history of previous febrile illness with vesicular rash on
97 palms and soles and also his sister had same symptoms, which suggested a contagious disease as an
98 etiology. Within the previous three months there were also two other young males with similar
99 testicular symptoms who were exploratively operated by the same urological team due to suspicion
100 of testis torsion. However, this could not be confirmed in the operation. Atypical clinical features as
101 well as admission and operation of the third patient within a quite a short period of time led to the
102 suspicion of a contagious viral disease. Vesicular exanthema on palms suggested enterovirus as a
103 possible etiologic agent. Because infection could not be suspected in the first two surgical cases, no
104 samples for microbiological detection were taken and thus a possible common exposure between
105 the cases could not be confirmed. However, anamnesis showed that before the admission to the
106 hospital, the patients had had symptoms of a viral infection, such as mild fever. Anyway, this
107 implies that epididymitis of viral origin might have been more common than could be suspected.
108 There are several enterovirus types circulating during epidemics, therefore we can't speculate about
109 the virus specific tropism of CV-A6 to epididymal tissue based on a single case.

110

111 Bacteria are the most common cause of epididymitis in adults, while orchitis is the classic
112 complication of viral infection (mumps) (13). A bacterial etiology is defined in 64 % of the cases
113 and they cause infections in young men under 35 years as common as in older men (14).

114 Epididymitis in boys under 14 years is considered to be mainly a post-infectious inflammatory
115 process (15).

116

117 Outcome of epididymitis is usually self-limiting and favourable, but mumps orchitis may lead to
118 testis atrophy and influence for infertility (13). Recently significant changes in sperm protein
119 composition have been found to occur following epididymitis (16).

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121 This is the first report to show that enteroviruses can be detected from epididymal fluid indicating
122 virus replication in the tissue. Epididymitis in young boys has been thought to be post-infectious
123 inflammatory phenomenon, which is based on the findings that the patients have had symptoms of
124 upper respiratory infections preceding scrotal symptoms (15). Also viruses have been detected from
125 nasopharyngeal specimens or stool samples and the patients have had higher virus antibody levels
126 in sera than controls (15).

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

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