Myocarditis Caused by Human Parechovirus in Adult

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The infectious etiology of myocarditis often remains unidentified. We report a case of myocarditis associated with human parechovirus (HPeV) infection in an adult. HPeV is an emerging pathogen that can cause serious illness, including myocarditis, in adults. Testing for HPeV should be considered in the differential diagnosis of myocarditis.

Infections with human parechovirus (HPeV) are rarely reported in adults. We report a case of myocarditis associated with HPeV infection in an adult.

The Study
During the summer of 2015, a 26-year-old man in Victoria, Australia, was admitted to Casey Hospital (Berwick, VIC, Australia) because of 4 days of fever, rigors, headache, dry cough, sore throat, myalgia, and a history of erythematous macular rash on arms bilaterally that had resolved by the time of admission. The patient smoked cigarettes and reported use of methamphetamine, but no other medical history was reported. He lived in a rural area but had no close contact with animals. He lived with 3 young children, including an 8-week-old infant who had recently had otitis externa.

At admission, he was febrile (temperature 38.2°C) and had sinus tachycardia (<130 beats/min). Results of a physical examination were otherwise unremarkable. Peripheral blood lymphocyte count was 0.70 × 10^9 cells/L (reference range 1–4 × 10^9 cells/L), C-reactive protein level 111 mg/L (reference value <5 mg/L), erythrocyte sedimentation rate 94 mm/h (reference value <10 mm/h), serum bilirubin level 49 µmol/L (reference value <20 µmol/L), and albumin level 24 g/L (reference range 35–45 g/L).

Microscopic analysis of cerebrospinal fluid (CSF) showed 2 × 10^4 polymorphonuclear cells/L, 2 × 10^4 lymphocytes/L, a total protein level of 0.5 g/L (reference range 0.1–0.3 g/L), and glucose and lactate levels within reference ranges. Blood and CSF cultures showed no bacterial growth. Because of a low leukocyte count, molecular studies for viruses (including enterovirus) were not performed for the CSF sample.

Fever and tachycardia persisted for 5 days and chest discomfort and dyspnea developed. A transthoracic echocardiogram showed a mildly dilated left ventricle with an ejection fraction of 15%. There were no valvular vegetations. Peak creatine kinase level was 713 U/L (reference value <230 U/L), and troponin level was 15.28 µg/L (reference value <0.080 µg/L).

The patient was given intravenous benzylpenicillin and oral doxycycline as empirical therapy for possible bacterial infection; Q fever and leptospirosis were considered possible diagnoses. Fever and chest discomfort improved, and he was discharged 7 days after admission. Two weeks later, the patient was well and had minimal dyspnea.

Throat swab specimens were obtained on day 6 of illness, and rectal swab specimens were obtained on day 8 of illness. Specimens were tested for enterovirus and HPeV RNA by reverse transcription PCR (RT-PCR) and primers specific for the highly conserved 5' untranslated region (1) (details for HPeV primers and probes are available on request). HPeV was detected in the throat swab specimen, but not the rectal swab specimen.

We attempted molecular typing of HPeV by using the method of Papadakis et al. (1) and primers AN353, AN355, AN357, AN358, and AN369 described by Nix et al. (2). However, typing was not successful because of low copy numbers, probably caused by specimens being collected late in the illness.

Multiple investigations showed no other infectious causes of myocarditis. Serologic results were negative for previous or recent infections with hepatitis A, B, and C viruses and HIV, as well as Leptospira spp., Coxiella burnetii, rickettsia, Treponema pallidum, and Toxoplasma spp. Serologic analysis showed evidence of previous infections with cytomegalovirus and Epstein-Barr virus. However, a convalescent-phase serum sample was not available for additional serologic testing.

A multiplex PCR (Respiratory Pathogens B; AusDiagnostics, Beaconsfield, NSW, Australia) was performed for a nasopharyngeal swab specimen. Results were negative for influenza A virus; A(H1N1)pdm09 virus; influenza B virus; respiratory syncytial virus; rhinoviruses/enterovirus; human parainfluenza virus 1, 2, and 3; adenovirus (groups B, C, E, some A, D); human metapneumovirus; Bordetella
pertussis and B. parapertussis; Legionella pneumophila
and L. longbeachae; Mycoplasma pneumoniae; and Chla-
mydia/Chlamydoghia spp. (including C. psittaci, C. pneu-
moniae, and C. trachomatis).

Conclusions
HPeVs were previously classified as a subgenus of echo-
viruses (3). Echovirus subtypes 22 and 23 were renamed
HPEV type 1 and 2; sixteen different types of HPEV thus far
have been identified. Serosurveillance studies showed that
by 2 years of age, ≤90% of children are infected with ≥1
type of HPEV (3). Infections with human parechoviruses
show various clinical manifestations, notably sepsis-like
disease and encephalitis in infants. A recent large outbreak
of HPEV type 3 infections in infants was reported in Aus-
tralia (4).

HPEV infections in adults are rarely reported. Mizuta
et al. reported 22 adults with myalgia, muscular weakness,
sore throat, orchiodynia, and increased levels of creatine
phosphokinase; 14 had HPEV type 3 infections confirmed
by virus isolation, positive RT-PCR results for throat swab
or stool specimens, or serologic analysis (5). HPEV was
also reported to be associated with flaccid paralysis and di-
rrehal illness in adults (6,7).

The rarity of HPEV infection in adults could be re-
lated to immunity conferred by previous exposure during
childhood to HPEV. Few seroprevalence data are available
for HPEV infections in adults. However, as part of an in-
vestigation of infant deaths associated with HPEV type 3
in Wisconsin, USA, limited serologic testing of 59 adults
demonstrated that infections were not common, suggesting
that either HPEV3 was a new pathogen being introduced to
this community, or that there was waning immunity, which
made antibody titers difficult to detect in adults (8).

The lack of documented reports of HPEV infection in
adults could also be caused by lack of widespread testing
for adults. HPEV RNA is not detected by routine enterovirus
PCRs and requires additional HPEV testing. The Victorian
Infectious Diseases Reference Laboratory (Melbourne,
VIC, Australia) routinely tests specimens for enterovirus
and HPEV when a request is made, regardless of the age of
the patients. During January 2015–May 2016, this labora-
atory tested 3,525 specimens for HPEV, of which 1,425
(40%) were obtained from adults. HPEV was detected by
RT-PCR in 5 (0.35%) of 1,425 specimens: 2 in throat swab
specimens, 2 in blood, and 1 in CSF. In comparison, 286
(13.6%) of 2,100 specimens from persons <18 years of age
were positive for HPEV; most (271, 94.8%) were from chil-
ren <1 year of age. This finding suggests that, although in-
creased testing for HPEV could increase the detection rate
of HPEV infection in adults, it is an uncommon infection in
the adult population. This finding is consistent with results
of a study from a reference laboratory in Scotland that test-
ed 3,739 CSF samples from persons of all ages and found
that although enteroviruses were common in adults, HPEV
infections were found exclusively in young infants (9).

Enteroviruses are recognized as a major cause of acute
myocarditis and are associated with ≤14% of cases (10).
Myocarditis associated with HPEV infections is rarely re-
ported (Table). This disease has been reported in 3 children
<2 years of age and 1 adolescent. Two of the patients were
immunosuppressed, 1 of whom died. A study of 109 pa-
tients infected with echovirus 22 (now HPEV subtype 1)
in Sweden included a case of myocarditis in a child; virus
was isolated from a stool sample and a major increase in
antibody titer was observed (11).

There is no proven effective therapy for HPEV infec-
tion. Intravenous immunoglobulin (IVIG) was used for 2
patients (Table). IVIG has been used for treatment of en-
terovirus infections, particularly in immunocompromised
patients (15), but the efficacy of IVIG might be limited for
therapy of HPEV infection because of low seroprevalence
in adults (8).

In summary, we report a case of myocarditis associ-
ated with HPEV infection in an adult. A large proportion
of cases of myocarditis has no identified infectious cause.

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Table. Characteristics of 5 patients with myocarditis caused by infection with human parechovirus*

| Patient (reference) | Age/sex | Underlying disease | Clinical features | Sample in which virus was detected | Subtype | Echocardiographic finding | Therapy | Outcome |
|---------------------|---------|--------------------|------------------|-----------------------------------|---------|-------------------------|---------|---------|
| 1 (11)              | NA/M    | NA                 | NA               | Stool, blood                      | ††      | NA                      | NA      | Died    |
| 2 (13)              | 14 mo/M | Congenital         | Congenital myocarditis | Stool, blood, myocardium, pericardial fluid | ††      | NA                      | None    | Died    |
| 3 (14)              | 6 wk/M  | AGG                | Myocarditis      | Stool                            | ††      | NA                      | None    | Survived |
| 4 (12)              | 16 y/F  | SLE, rituximab-induced HGG | Myocarditis, encephalitis | Stool, myocardium, CSF, stool | 3       | IVIG                    | Survived, prolonged neurologic recovery | Survived, Well at 6-mo follow up |
| 5 (this study)      | 26 y/M  | None               | Myocarditis      | Throat swab specimen              | Unknown | Dilated left ventricle, LVEF 15% | None    | Follow up |

*AGG, agammaglobulinemia; CSF, cerebrospinal fluid; HGG, hypogammaglobulinemia; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; NA, not available; SLE, systemic lupus erythematosus.
†Previously known as echovirus subtype 22.
Thus, testing of throat swab, stool, and blood specimens for HPeV should be considered for adults with myocarditis. HPeV is an emerging pathogen that can cause major illness, including myocarditis, in adults.

Dr. Kong is an infectious diseases fellow at Monash Health, Melbourne, Victoria, Australia. His primary research interest is emerging virus infections.

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