American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e928099
DOI: 10.12659/AJCR.928099

Received: 2020.08.20
Accepted: 2020.11.09
Available online: 2020.11.19
Published: 2021.01.13

Bocavirus Infection in a Young Pregnant Woman: A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 22-year-old
Final Diagnosis: Dilated cardiomyopathy • human bocavirus pneumonia • multi organ failure/septic shock
Symptoms: Cough • fever • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course

Background: Human bocavirus (HBoV) is a parvovirus found primarily in children and was first identified in 2005. It usually causes mild upper- and lower-respiratory tract infections. HBoV infection seems to be rare during adulthood, probably due to high antibody titers resulting from childhood infection and seroconversion. The clinical significance, possible complications, and consequences of an adulthood infection are still unclear. Furthermore, the consequences of HBoV infection during pregnancy are seldom reported in the literature.

Case Report: We report the case of a 22-year-old pregnant woman in her third trimester who presented with a 1-week history of fever and cough followed by progressive shortness of breath. She was treated initially as a case of severe pneumonia; however, her condition deteriorated rapidly, resulting in hypoxic respiratory failure that required intensive care support. The patient was found to have dilated cardiomyopathy on echocardiography, and her fetal ultrasound showed no fetal heart activity; subsequently, labor induction for stillbirth was performed. An extensive workup for an underlying cause was unrevealing apart from positive respiratory viral PCR assay for human bocavirus, performed twice. A provisional diagnosis of HBoV pneumonia complicated by dilated cardiomyopathy, stillbirth, and multiorgan failure was made. Fortunately, the patient had a good recovery and was discharged home in good clinical condition.

Conclusions: In addition to severe pneumonia, HBoV infection may result in other life-threatening complications. Although the infection is rare during adulthood, infection in a pregnant woman should be taken seriously and close monitoring of such patients is advised.

MeSH Keywords: Cardiomyopathy, Dilated • Human bocavirus • Pregnancy Complications

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/928099

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Human bocavirus 1 (HBoV1) was first described in 2005 by Allander in Sweden [1]. It has been identified in nasopharyngeal specimens from children with respiratory tract infection, and was classified as a member of the family Parvoviridae (subfamily Parvovirinae), which are small, non-enveloped viruses with single-stranded DNA [2]. The virus has 4 serotypes (HBoV 1–4); serotype 1 is associated with respiratory tract infection [3,4], while serotypes 2-4 are usually detected in fecal samples [5].

HBoV is frequently co-detected with other respiratory viruses, and this viral co-detection has started a debate about whether HBoV is a passenger rather than true pathogen, but emerging evidence supports its possible pathogenicity [6–9].

The clinical manifestations of HBoV infection in children are diverse. HBoV1 infection can range from self-limited influenza-like illness in most cases [10] to life-threatening conditions like respiratory failure, pneumothorax, and myocarditis [11–14]. Additionally, various dermatological manifestations are reported to be associated with HBoV infection [15,16], but most of the cases require only supportive care, as there is still no specific targeted therapy [17,18].

HBoV is rarely detected in adults due to the high rate of seroconversion during early childhood [19–23]. Previous studies, mostly case reports [12,24], have shown that HBoV can cause severe pneumonia in immunocompromised adults and possibly causes myocarditis in the elderly.

The clinical significance, possible complications, and consequences of adulthood infection are unclear, and the consequences of HBoV infection during pregnancy have seldom been reported in the literature.

Here, we report the case of a young pregnant woman who presented with clinical features of severe pneumonia and required intensive care support, complicated by dilated cardiomyopathy, fetal death, and multiorgan failure. An extensive workup for possible infectious causes was negative, apart from a positive respiratory viral panel for HBoV.

Case Report

A 22-year-old woman at 36 weeks' gestation (gravida 2, para 1) presented to the Emergency Department in Qatar late in the winter of 2015 because of a 1-week history of flu-like symptoms, fever, muscle pain, dry cough, and diarrhea, was followed by progressive shortness of breath a few days later. She was the mother of a 2-year-old child, with a previous uneventful pregnancy. She gave a history of a travel to her home country (Oman) 2 weeks prior to her presentation. She reported no history of sick contacts. She was treated for Hodgkin's lymphoma 10 years prior to her presentation and was in remission since then, with no history of recurrence. She was being followed in her antenatal care in Oman, and there was no available documentation about her pregnancy follow-up. Upon arrival to the Emergency Department, she was febrile, with a temperature of 38.0°C. Her blood pressure was 140/68 mmHg, pulse rate 90/min, and oxygen saturation 96% on room air. A physical exam was remarkable for gravid uterus (in keeping with gestational age), bilateral basal lung crackles, and a macular rash over the hands and feet, including her palms and soles (**Figure 1**). The initial laboratory evaluation was significant for mild leukocytosis (white blood cell 12.7×10^3/uL), mild anemia (hemoglobin 10 gm/dL), and a normal platelet count of 354×10^3/uL. C-reactive protein (CRP) was elevated at 110 mg/L, and she had a normal serum procalcitonin level of 0.16 mg/L. Kidney and liver functions were normal. Urine, sputum, and blood bacterial cultures did not grow any pathogens. A chest radiograph revealed cardiomegaly with increased vascular markings, signs of congestion, and right middle- and lower-lobe opacities (**Figure 2**).

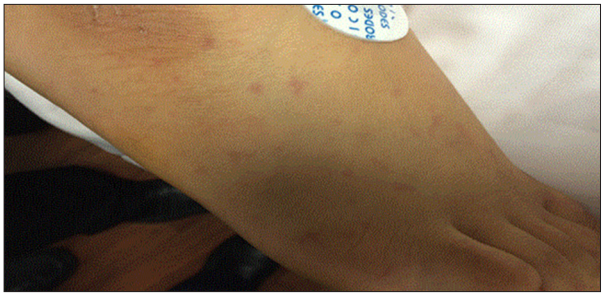

Figure 1. Macular rash over hands and feet, including palms and soles. Physical exam showed a 2–3 mm red non-blanchable macular rash over her hands and feet, including palms and soles. The rash was not painful or itchy.

An ultrasonographic examination of the abdomen showed no fetal heart activity. Her condition deteriorated rapidly within a few hours of arrival, with acute hypoxemic respiratory failure and hypotension. Endotracheal intubation was performed, and she was connected to a mechanical ventilator and started on vasopressors. Piperacillin-tazobactam and moxifloxacin were started for the possibility of severe pneumonia. Transthoracic echocardiography revealed a dilated left ventricle with a very low ejection fraction of 20%. Labor induction was performed for a stillbirth. The course of the illness was complicated by acute kidney injury (AKI), with serum creatinine reaching 390 mmol/L, disseminated intravascular coagulation, and acute liver injury, with INR of 2.2, alanine aminotransferase (ALT) of 2000 IU, and aspartate aminotransferase (AST) of 3255 IU. All

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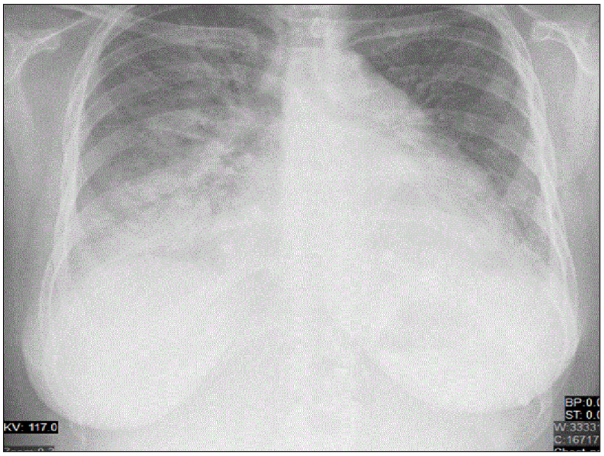

Figure 2. Chest radiograph at admission. Chest X-ray revealed cardiomegaly, increased vascular marking, congested lung fields, and cephalization of pulmonary vasculature, in addition to right middle- and lower-lobe patchy opacities.

other test results were negative, including peripheral smear for malaria parasites, human immunodeficiency virus (HIV) serology, viral hepatitis A/B/C/E serology, brucella antibody titer, urine legionella antigens, anti-nuclear antibodies (ANA), and thyroid function tests. Serum quantitative polymerase chain reaction (qPCR) for Epstein-Barr virus (EBV), parvovirus B19 virus, human herpes virus 6, and measles virus were requested and came back negative.

A nasopharyngeal swab was done on admission and sent for viral panel analysis to our National Reference Virology Laboratory, Department of Pathology and Laboratory Medicine (DPLM) in Hamad Medical Corporation, Qatar. The nasopharyngeal swab came back positive for human bocavirus twice on repeated testing with 2 consecutive samples 24 h apart. The test method used for viral panel analysis was classic multiplex real-time polymerase chain reaction (PCR) (using FTD™ Respiratory pathogens 21 for detection of pathogen genes by TaqMan® Technology) for detection of influenza A, influenza A (H1N1), influenza B, coronaviruses NL63, OC43, and HKU1, parainfluenza 1–4, human metapneumovirus A and B, rhinovirus, respiratory syncytial viruses A and B, adenovirus, enterovirus, parechovirus, bocavirus, and *Mycoplasma pneumoniae,* including internal control. We made a provisional diagnosis of pneumonia severely complicated by dilated cardiomyopathy, stillbirth, and multiorgan failure, with a presumptive etiology of HBoV viral pneumonia, as no alternative causative agent could be identified. During her hospital stay, she had a good recovery, with improvement in kidney and liver function and other blood parameters. She was subsequently extubated and disconnected from mechanical ventilation. Her critical care myo-neuropathy that resulted from her prolonged stay in the Intensive Care Unit improved with physiotherapy, and she was able to ambulate independently. She was discharged home in good clinical condition.

Discussion

Human bocavirus 1 (HBoV1) was first described in 2005 by Allander in Sweden [1]. It has been identified in nasopharyngeal specimens from children with respiratory tract infections. Analysis of the gene sequences showed similarities to bovine and canine parvoviruses, and the virus was named human bocavirus (HBoV), which became a member of the family Parvoviridae (subfamily Parvovirinae [2], genus Bocaparvovirus, which is a small, non-enveloped, single-stranded DNA virus. Globally, the prevalence of HBoV1 in young children with respiratory tract infections ranges from 10% to 33% [3]. The virus has 4 serotypes (HBoV 1–4), in which serotype 1 is associated with respiratory tract infection [4], while serotypes 2–4, which are referred to as enteric bocaviruses, are usually detected in fecal samples, with unclear evidence of its pathogenicity and ability to cause gastroenteritis [5].

It is well established that HBoV1 infections occur among children younger than 5 years old, especially in infants (under 2 years of age), in whom it has been reported mainly as a pathogen affecting the respiratory tract [6]. However, it is unclear whether HBoV1 alone can cause an infection with subsequent viral shedding, viremia, and persistence in different organs [7]. HBoV infections are very often accompanied by other co-pathogens, which suggests HBoV could be a passenger rather than a pathogen in airway infections [8], although other studies suggested that HBoV can cause serious mono-infections [9].

Most pediatric patients present with fever, rhinorrhea, cough, and wheezing. The virus is usually detected in nasopharyngeal swabs, serum, and fecal samples by polymerase chain reaction (PCR). Viremia was reported in 10% of the cases with confirmed lower-respiratory tract infections with HBoV1 [10].

HBoV1 infection can range from self-limited influenza-like illness in most of the cases, to life-threatening conditions, with many reported cases associated with serious complications, including respiratory failure, pneumothorax, and myocarditis [11–13]. People at high risk for respiratory problems may require intensive care support and experience significant morbidity [14].

The reported associated skin manifestation among infected children include blanching maculopapular erythema on the chest, and some of these patients also had macular erythema of the face [15], in addition to 1 child with HBoV who had gastroenteric symptoms, and the clinical diagnosis was exanthema subitum [16].

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Regarding treatment, most patients require only supportive care, as there is still no specific targeted therapy [17], and there has been only 1 case report in which antiviral treatment was associated with the elimination of HBoV, in a patient who had co-infection with HHV-6 and was treated with Cidofovir [18].

Despite the well-described molecular and clinical characteristics of HBoV infection among children, its presentation in adulthood is quite uncommon due to the high rate of seroconversion during early childhood, which can reach 100% in children older than 2 years [19].

A study of 1952 serum samples collected consecutively at 3- to 6-month intervals from 109 healthy children starting from infancy to early adolescence found that primary HBoV1 infection (as indicated by seroconversion) appeared in 102 (94%) of 109 children at a mean age of 2.3 years; the remaining 7 children were IgG antibody-positive from birth [20]. Nevertheless, HBoV1 in adults is rare. A study found that when HBoV serotypes were discriminated to avoid cross-reactivity using enzyme-linked immunoassay (ELISA) testing, 17.6% of the adults who were positive for IgG against HBoV1, 2, 3, or 4 based on the ELISA results were negative for IgG against all 4 HBoV based on the competition ELISA (cELISA) results. This indicated that a high degree of antigenic cross-reactivity between all serotypes and subsequent infection could occur due to declining antibody levels in individuals with low IgG levels [21].

Given the high seroconversion, data on adult HBoV infection characteristics are limited, and its virulence or other adverse clinical outcomes are still unclear.

A large study in Guangzhou, southern China, analyzed the characteristics and clinical manifestations of HBoV-positive samples from acute respiratory tract-infected patients with a wide age distribution. The detection rate in children was significantly higher than in adults ($P<0.001$). HBoV was detected in only 4 adult patients (4/1014) (0.4%), which suggests that older people were also susceptible to HBoV infection, although with much lower positive rates. These 4 adult patients also presented with systemic influenza-like symptoms, suggesting that HBoV infection in adults is a more complex and serious problem than in children [22]. A low prevalence rate was also shown in a study conducted in 3 university-affiliated hospitals in the province of Quebec, Canada [23], in which HBoV was detected in nasopharyngeal samples from 1 (0.8%) of 126 symptomatic adults, a 71-year-old COPD patient with an acute exacerbation with no other bacterial or other viral pathological evidence who was hospitalized for 11 days.

Due to its rarity among adults, the severity and other extrapulmonary manifestation are still unclear. The first case report of an HBoV respiratory tract infection in an adult immunocompromised patient in 2006 [24] found that HBoV is associated with illness during adulthood in immunocompromised patients, who can have serious complications. This was supported by another study [12], which showed severe respiratory tract infection in another immunocompromised patient.

It is unclear whether HBoV1 has other extrapulmonary complications in adults, particularly among pregnant women. There are ongoing studies regarding the possible association of HBoV with stillbirth and abortions; 2 studies failed to detect HBoV in stillborn children or hydrops fetalis [25,26]. However, it was shown that veterinary bovine and canine parvoviruses, which are closely related to HBoV 1–4, are responsible for abortions in their natural hosts (cattle and dogs) [27–29].

A study of 172 patients was conducted to evaluate the relationship between HBoV infection and abortions in human models; aborted tissues and placenta samples were examined histologically, showing that 25% of abortions had a positive result for HBoV DNA, but these positive PCR results were combined with histological signs of HBoV infection such as cytopathic effects in only 1 case, and the virus induced only minor or moderate effects in infected cell culture. Therefore, the study could not determine if the miscarriage was caused by HBoV or was just accompanied by the virus, although the results suggested a causal relationship because HBoV was not detected in the control cohort [30].

There is limited information on the role of HBoV in cardiac diseases, particularly in pregnant women, although many cases of myocarditis were reported in children with different clinical presentations and outcomes, which raised the possibility of a causal relationship [31–33]. HBoV can induce significant expression cardiac inflammatory cytokines with interlukin-1β and interlukin-6 in myocyte cells [34]. Another study assessed the prevalence and quantity of HBoV and B19 virus on histopathological examination of heart tissue in patients who did not experience any viral-related heart disease. The study found a 96% positive serology for IgG against HBoV, but none of the serum samples and only 5% of heart tissue samples showed detectable HBoV DNA, suggesting that HBoV lacks lifelong persistence in the heart [35].

We found only 1 case report of viral myocarditis with subsequent cardiomyopathy, in an 85-year-old patient, possible related to HBoV, as no other alternative diagnosis could be elicited [36]. Another report found that HBoV could be a potential cause for usual interstitial pneumonia (UIP) and possibly even heart disease, as HBoV was detected in myocardial tissue through autopsy [37].

Conclusions

As no other possible etiological cause for our patient's presentation could be found, we concluded that in addition to severe

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pneumonia, HBoV infection may result in other life-threatening complications during pregnancy, including cardiomyopathy and multiorgan failure. Although the infection is rare during adulthood, infection in a pregnant woman should be taken seriously and close monitoring of such patients is advised. Further studies are needed to determine to what extent exposure to this virus in general or in co-infections can lead to severe disease or death during immunosuppression or in the elderly. An interesting possibility and topic for further research is to what extent HBoV1 DNA levels at various sites are associated with virulence or adverse clinical outcomes.

Acknowledgments

The authors are indebted to Dr. Muna Al-Maslamani for her continuous support during the preparation of this manuscript.

Conflict of interest

None.

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