INSTRUCTIVE CASE

Believing bocavirus: A rare case of life-threatening acute respiratory distress syndrome requiring extracorporeal membrane oxygenation

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Case Report

A previously healthy 6-year-old girl presented to a regional hospital with a 24-h history of cough, lethargy and fever. On presentation to the emergency department, she was febrile (38.1°C) with mild subcostal recession and reduced air entry in the left lung base (respiratory rate 28/min, oxygen saturation 92% in room air). Chest radiograph revealed early left lower lobe consolidation (Fig. 1). She was admitted to the ward for benzylpenicillin (45 mg/kg q6h intravenous injection (IVI)) and low-flow oxygen (1 L/min). Over an 8-h period, she had worsening respiratory distress, dramatic progression of chest radiograph appearances (Fig. 1) and required escalation to high-flow oxygen (2 L/kg) via nasal prongs. She was mechanically ventilated prior to transfer to a tertiary paediatric centre for the management of respiratory failure. Full blood count revealed haemoglobin 122 g/L, white cell count 16.4 × 10^9/L, platelet count 230 × 10^9/L, neutrophil count 14.7 × 10^9/L, lymphocyte count 0.6 × 10^9/L. C-reactive protein 46 mg/L, procalcitonin 1.6 ng/mL. Renal, liver functions and coagulation profile were all within normal ranges. Antimicrobial therapy was broadened to clindamycin (10 mg/kg/q8h IVI), cefotaxime (50 mg/kg/q8h IVI) and azithromycin (10 mg/kg/q24h IVI). Upon arrival to our tertiary paediatric centre, she was haemodynamically stable, but in severe respiratory failure with an oxygenation index of 45. A diagnosis of acute respiratory distress syndrome (ARDS) was made. Respiratory support was escalated to high-frequency oscillatory ventilation and inhaled nitric oxide. A chest ultrasound demonstrated dense left-sided consolidation and a small pleural effusion. Oseltamivir (45 mg/q12h orally) was added, and trimethoprim-sulphamethoxazole (5/25 mg/kg/q6h IVI) for possible Pneumocystis jirovecii pneumonia in light of lymphopaenia and respiratory failure.

Her childhood immunisations were up to date. There was no history of travel or contact with birds. She did not have a history of asthma or previous hospitalisations. She then developed refractory hypoxia (arterial blood gas: pH 7.0, pCO2 104 mmol/L, SO2 83% (oxygen index 51)) and commenced on veno-venous extracorporeal membrane oxygenation (ECMO) via right jugulo-vena cava cannulation. A chest radiograph demonstrated worsening appearances with new right upper lobe densities (Fig. 1). A transthoracic echocardiogram showed a structurally normal heart, normal ventricular function, no vegetations and normal pulmonary artery pressures. Bronchoscopy and bronchoalveolar lavage (BAL) revealed normal airways, copious purulent endobronchial secretions with moderate polymorphonuclear cells and no bacterial or fungal growth but secretions from the left lingula lobe were positive for HBoV1-4 by polymerase chain reaction (PCR) with a cycle threshold (Ct) value of 13.38 (cutoff Ct value 36). Nasopharyngeal aspirate also demonstrated mono-detection of HBoV1-4. With the exception of HBoV1-4, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila, Bordetella pertussis/parapertussis, adenovirus, enterovirus, coronaviruses NL63/229E/OC43, influenza A and B, human metapneumovirus, parainfluenza,1–4 rhinoviruses and respiratory syncytial virus A and B were all negative. In both the nasopharyngeal aspirate (NPA) and BAL, only HBoV1-4 was detected on the full respiratory panel. P. jirovecii pneumonia PCR on BAL and M. pneumoniae IgM were negative and blood cultures sterile. Human immunodeficiency virus antibody was negative.

Over the course of 5 days, she remained in single organ failure, was weaned from ECMO support and decannulated on day 6. She made a rapid recovery, was extubated to high-flow oxygen via nasal prongs on day 9, discharged from intensive care unit (ICU) the following day and made a complete recovery with

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normal chest radiographic appearances (Fig. 1). She completed 10 days of cefotaxime and clindamycin. The lymphopaenia resolved prior to discharge and is presumed to be due to the viral illness. At the 6-week follow up, she remained in good health with normal growth and development. Unfortunately immune testing (lymphocyte subsets and immunoglobulins) were not done during convalescence. Further follow up for this was arranged with a local paediatrician.

HBoV1-4 PCR on blood taken prior to the institution of ECMO was positive (Ct value = 29.58) (Table 1). HBoV1-4 PCR on blood taken during convalescence (day 8) was negative (Ct value = 41.5). One week following our patient’s admission, her 4-year-old brother developed fevers, tachypnoea, wheeze and hypoxia. His chest radiograph showed bilateral alveolar opacities. NPA and blood PCR were positive for HBoV1-4 (Ct value = 22.28 and Ct value = 31.83), respectively. Only HBoV1-4 and not any other viral or bacterial target, was detected in all samples from the index case and sibling.

**Discussion**

Human bocavirus (HBoV), a small non-enveloped DNA virus, belongs to the family *Paroviridae* and was discovered in 2005 in NPAs of young children with acute respiratory tract infections.

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**Fig. 1** Serial chest radiographs of bocavirus pneumonia in a 6-year-old girl admitted with life-threatening acute respiratory distress syndrome. (a) Day 1 of illness (at presentation to the emergency department). (b) Eight hours after presentation; dense lingua consolidation/collapse and left lower lobe consolidation. (c) Day 2 of illness, post-extracorporeal membrane oxygenation cannulation, complete left sided consolidation with new right upper lobe pulmonary infiltrate. (d) Complete resolution of consolidation on day 10 of illness. Discharged the following day.
(RTIs). Four different species of bocavirus (HBoV1-4) have been proposed with HBoV1 being associated with RTIs. Unlike most respiratory viruses occurring in childhood, there is no clear seasonality of HBoV infections. It however remains controversial whether HBoV1, as a single pathogen, causes disease as it is found in asymptomatic individuals, has prolonged shedding from the respiratory tract of up to 1 year following primary infection, and is found as a co-pathogen in up to 75% of children with lower RTIs. Co-detection with other viruses raises the question whether HBoV1 has an active or synergistic role in respiratory infections. Studies evaluating potential viral-viral interactions are lacking. Therefore, attributing disease to HBoV1 alone is difficult and requires fulfilling of several microbiological criteria. Evidence is now emerging that HBoV1 alone can be a rare cause of acute severe RTIs necessitating critical care management.

The clinical manifestations of RTI caused by HBoV1 include cough, fever, dyspnoea, vomiting and rhinorrhea. Primary infection usually occurs in early childhood with sero-prevalence reaching 90% in children by 3 years of age. RTIs caused by HBoV1 are clinically indistinguishable from other common respiratory viruses in childhood. Children hospitalised with HBoV1 induced RTIs are often diagnosed with bronchiolitis, pneumonia or acute exacerbations of asthma. Children admitted to ICU with HBoV1 are older than those admitted with RSV (median 24 vs. 2 months). Although rare, it is notable that there are increasing reports of HBoV1 causing severe, life-threatening respiratory infections which require critical care support. This included a previously reported case fatality in an 18-month-old child with chronic lung disease of prematurity. To our knowledge, our case is only the second case describing the use of ECMO support for life-threatening RTI caused by HBoV1 and the first describing critical ARDS caused by HBoV1.

HBoV1 infection induces inflammasome activation, caspase 1-induced cell death, interleukin and interferon (IF)-γ production which have been implicated in the pathophysiology of ARDS. In acute HBoV1 infections, C-reactive protein concentrations and white blood cell counts are usually within normal limits. Chest radiograph appearances in our case were unique as peribronchial, interstitial infiltrates and atelectasis are most commonly described.

As multiple viruses are often detected in respiratory samples, diagnosing RTI due to HBoV1 requires multiple microbiological criteria. Current expert guidance recommends that HBoV1 infection should not be diagnosed on the basis of HBoV1 DNA detection from respiratory samples alone. Additional diagnostic approaches include quantitative HBoV1 DNA analysis (>10^6 copies/mL) of nasopharyngeal secretions, serology (IgM, low IgG avidity or a more than or equal to fourfold IgG titre rise) and/or HBoV1 antigen detection in nasopharyngeal secretions. With advancements in diagnostic approaches, clinicians have been able to diagnose acute HBoV1 infection with greater confidence, which might explain the increasing reports of acute paediatric infections caused by HBoV1.

Primary HBoV1 infection could be distinguished from virus shedding by analysis of anti-HBoV1 antibodies. HBoV1 serology is not yet available anywhere in Australia. In the absence of HBoV1 serological and antigen testing, DNA in blood could be used to diagnose HBoV1 RTI. The presence of HBoV1 viraemia is usually specific for acute HBoV1 infection. Viraemia is rarely detected in controls, has a short duration and rarely lasts beyond the first week of acute illness. We were able to demonstrate HBoV viraemia during the acute illness (day 2) which became undetectable during recovery (day 8). Significantly higher viral loads have been demonstrated in respiratory samples of children admitted to ICU with HBoV1-induced RTI. Our laboratory currently provides semi-quantitative HBoV 1–4 viral loads only. Low Cts clearly below the cut off (Ct value cutoff – 36) in all respiratory samples (Ct value 17.6 – NPA, Ct value 13.3 – BAL) and blood (Ct value – 29.6) would indicate significantly high viral loads. The lack of evidence for other viruses or bacteria on multiple respiratory samples (BAL, NPA) provided support for HBoV1 as the aetiology. Only one set of BAL washings were taken from the lingula lobe as the child was too unstable to extend the procedure longer than necessary and take samples from other lobes. In the absence of other positive results, mono-detection of HBoV1-4 from multiple respiratory samples separated in time and location, combined with PCR positivity in blood, we believe this to be strong evidence of true mono-infection with HBoV1. It is notable, however, that existing reports of severe disease attributed to HBoV1 has been in children with underlying conditions or immunocompromised status and that the typical age of infection for HBoV1 primary infection is under 2 years of age. It is therefore highly unusual that a previously well 6-year girl develops HBoV infection of this magnitude. One hypothesis is the potential role of unique host–virus interactions in causing disease however this remains to be elucidated.

Transmission of HBoV1 occurs via respiratory secretions and secondary HBoV1 infection has occurred within families. The younger sibling of our patient, who was a household contact developed fever, cough, wheeze and hypoxia 1 week after our index case. The sibling’s disease was less severe requiring typical

### Table 1: Bocavirus polymerase chain reaction testing in sibling pair admitted with respiratory illnesses

| Index case Ct value | Bocavirus result | Sibling Ct value | Bocavirus result |
|---------------------|------------------|------------------|------------------|
| NPA 17.63 (day 2 of illness) | Positive 22.28 (day 2 of illness) | Positive | BAL 13.34 (day 3 of illness) | Negative 31.83 (day 2 of illness) | Positive |
| Blood 29.58 (day 2 of illness) | Positive | NP | Blood 41.50 (day 8 illness) | Negative | Testing during recovery |

† Positive result deemed as Ct value less than 36 as per validated cutoff for respiratory samples. ‡ Positive result deemed as Ct value less than 36 as per validated cutoff for respiratory samples. There are currently no cutoff Ct values for blood. BAL, bronchoalveolar lavage; CT, cycle threshold; NP, not performed; NPA, nasopharyngeal aspirate.
supportive management (oxygen and bronchodilators) only. As in the index case we demonstrated HBoV 1–4 monodetection on NPA, however, viral loads were lower (Ct value 22.28 – NPA, Ct value 31.83 – blood). There is currently no specific antiviral treatment available for HBoV1 infections. A post-hoc analysis of a randomised controlled trial demonstrated that prednisolone was ineffective at reducing hospital admission stay in wheezing children with HBoV1 infection. Supportive management for HBoV1 bronchiolitis or pneumonia have been the mainstay of treatment. This rare case report adds new knowledge that the extent of respiratory support in extreme cases of HBoV 1–4 induced ARDS may require consideration of veno-venous ECMO.

HBoV1 is emerging as a rare cause of life-threatening lower RTI in children. Clinicians should be aware of varying presentations and the techniques to diagnosing acute HBoV1 infection in children.

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