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High-dose glucocorticoid treatment of near-fatal Bocavirus lung infection results in rapid recovery

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Summary / “Take home” message

Human Bocavirus (HBoV) has to be considered as life-threatening pathogen in adults with atypical pneumonia. Pulsed high-dose glucocorticoid-treatment may be beneficial in patients suffering from severe pulmonary disease caused by HBoV or other viruses.
Main Text

Human Bocavirus (HBoV), which belongs to *Parvoviridae*, is a well-defined pathogen of respiratory infections particularly in young children [1]. In contrast, the frequency of HBoV infections in adults with respiratory symptoms is virtually unknown, and its causative role in respiratory failure is debated [1, 2]. Furthermore, the observation that dexamethasone is beneficial in Covid-19 patients with respiratory failure requiring respiratory support has gained great interest [3]. However, whether glucocorticoid-treatment (GT) is useful in other severe viral respiratory diseases is a matter of controversy [4].

Here, we report on a 58-year-old, obese (BMI 35 kg/m²; ECOG 1), caucasian male who presented at Charité University Hospital in 25th of February 2020 with a 6-day history of fever and shortness of breath. Three months earlier, he had received BEAM (carmustine (BCNU), etoposide, cytarabine, melphalan) high-dose chemotherapy and autologous stem cell transplantation (autoSCT) for relapsed Hodgkin’s lymphoma, resulting in complete remission. Relevant medical history included psoriasis, diabetes mellitus type 2, permanent atrial fibrillation and COPD GOLD II, with no relevant previously documented pulmonary structural alterations. Concomitant medication on admission consisted of acyclovir, pantroprazole, digitoxin, bisoprolol, sitagliptin, metformin, insulin and acitretin, all not considered as causative for the clinical symptoms. On admission, peripheral oxygen saturation demonstrated hypoxemia (SpO2 88%), C-reactive protein (CRP) level was 50.9 mg/L (normal range [<5 mg/L]) and chest radiograph disclosed diffuse reticular, interstitial infiltrations of the lung. As the patient deteriorated accompanied by further CRP increase to 92.9 mg/L during a 7-day course, from 25th of February until 3rd of March, of antibiotic treatment with piperacillin/tazobactam and ciprofloxacin, a subsequent lung CT scan (figure 1a) revealed bilateral pulmonary infiltrates with interstitial pattern, ground-glass opacities, (preexisting) bullae and consolidation in the upper-left lobe. Small-volume bronchoalveolar lavage (BAL) and lung biopsy were performed. At 5th of March, the patient finally required mechanical ventilation due to respiratory failure without signs of overt sepsis with an initial positive end-expiratory pressure of 5 cm H₂O; PaO2:FiO2 was 136 mmHg suggesting moderate acute
respiratory distress syndrome (ARDS). Extended examinations of the BAL for infectious pathogens (bacterial culture and microscopy; PCR-based respiratory panel-analyses including various infectious agents: viruses [adenovirus, HBoV, cytomegalovirus (CMV), coronavirus including SARS-CoV-2, Epstein-Barr-virus (EBV), entero/rhinovirus, human herpesvirus 6 (HHV6), herpes simplex virus (HSV)-1/2, influenza virus A/B, metapneumovirus, parainfluenzavirus 1-4, respiratory syncytial virus (RSV) A/B, varizella zoster virus (VZV)], bacteria [Bordetella spp, Chlamydia spp, Legionella spp, Mycoplasma spp] and Pneumocystis jirovecii) revealed positivity for HBoV (and low-level detection of EBV [2390 cp/mL] in the BAL but not on the blood, judged as not clinically relevant) but no other pathogens.

We considered HBoV-infection followed by excessive immune response, possibly aggravated by immune reconstitution after autoSCT, as underlying pathogenic events. High concentration of HBoV genome-copies (3.2x10^8 copies/mL; BAL), HBoV-detection by fluorescence in situ hybridization (FISH) (figure 1b) and pronounced T-lymphocytic infiltrates (figures 1c and 1d) in the lung tissue confirmed this scenario. Given the lack of HBoV-specific treatments, we aimed to mitigate the immune reaction and subsequent pulmonary damage by pulsed high-dose GT (5th of march day 1, 500 mg prednisolone; days 2 and 3, 1000 mg methylprednisolone), followed by rapid reduction to 20 mg per day prednisolone and tapering. Respiratory parameters and radiologic findings improved rapidly (figures 1e and 1f) allowing termination of mechanical ventilation on day 4 (8th of march) of ICU treatment and discharge on 17th of march. In parallel to the clinical improvement, CRP-values rapidly decreased and remained normal. A CT scan two months after treatment confirmed complete resolution of all infiltrates (figure 1g).

Given the virtually unknown frequency of HBoV in adult patients with respiratory symptoms [1], we retrospectively analyzed a total of 5,328 consecutive adult respiratory samples, mainly consisting of tracheobronchial secretions and BALs and which were all examined by PCR-based respiratory panel-analyses, for HBoV. We identified 17 HBoV-positive patients, most of them heavily immunocompromised. Given the reconstitution of white blood cells (4.45/nL [3.90-10.50]) with normal neutrophils (3.03/nL [1.50-7.70]) and slightly reduced lymphocytes (0.95/nL [1.10-4.50]), even though
platelets (30/nL [150-370]) and hemoglobin (8.9 mg/dL [13.5-17.0]) were reduced at admission, as well as almost normal immunoglobulin levels (IgG 6.61 g/L [7.00-16.00]; IgA 1.72 [0.7-4.00]; IgM 0.30 [0.40-2.30]) at the time of HBoV-induced respiratory failure, we judged our patient as largely immunocompetent. Thus, even though rare, HBoV has to be considered as life-threatening pathogen in adults with atypical pneumonia and should be included in the respective diagnostic work-up with HBoV-DNA quantification, if positive.

Only recently, it has been demonstrated that dexamethasone is beneficial in Covid-19 patients with respiratory failure requiring respiratory support [3], however the benefit of GT in other severe viral respiratory diseases is unclear [4]. In contrast to the dexamethasone-scheme used in the RECOVERY trial in Covid-19 patients (6 mg once daily for up to 10 days), we applied a pulsed high-dose GT scheme deduced from treatment of autoimmune-diseases. Of note, the application of such pulsed ‘very high-dose’ GT is supposed to extend the GT mode of action compared to lower doses [5][6]. We assume that this short-term high-dose GT has effectively dampened the detrimental virus-induced immune response, most likely by GT-induced cell death of immune effector cells including infiltrating T cells and anti-inflammatory effects by modulation of monocyte and macrophage function [7][8]. Furthermore, GT can inhibit fibroblast proliferation and support the clearance of inflammation-induced tissue damage [7]. We are aware of GT-induced side effects, that corticosteroid treatment of ARDS- or severe acute respiratory syndrome (SARS)-patients or patients suffering from viral pneumonia has generated conflicting results [4][5][9][10][11], and that prolonged intake of corticosteroids predisposes for invasive aspergillosis in the context of severe influenza infection [12]. On the other hand, short pulsed high-dose GT is used since decades for the treatment of various severe autoimmune diseases with limited and well-known side effects [13], the reason for that we decided to use such a ‘very high-dose’ short-term scheme and not a lower-dose longer-lasting scheme for our patient. We believe that in selected patients, in which the virus-induced immune response is profound and likely more harmful to lung tissue than damage by the virus itself, and in which fatal lung damage has not yet passed the point of no return, GT may preserve lung tissue and function. Of note, most recently it has been shown that severe Covid-19 patients benefit from
pulsed methylprednisolone administration, if given during the early phase of pulmonary infection [14]. Thus, high-dose GT may be beneficial in patients suffering from severe pulmonary disease caused by HBoV, as demonstrated in our case, or other viruses.

References


Figure legends

FIGURE 1.
Radiomorphologic and pathologic-anatomic findings of a patient with near-fatal human Bocavirus infection. a) CT-scan after a 7-day-course of antibiotics-therapy shows bilateral upper lobe interstitial pattern with ground-glass opacities. b) HBoV-specific FISH in lung biopsy. Head and tail HBoV genome-regions were detected with specific fluorescence probes, and tissue was counterstained with DAPI. Yellow and orange dots (arrows) indicate co-detection of head and tail regions of HBoV-DNA. c) Lung biopsy showing fibroblast proliferation (arrows in c); H&E-staining). d) Strong infiltration with T cells (CD3-staining in brown) in the lung tissue reflecting excessive immune response. e, f) Chest radiographs (anteroposterior view) e) at initiation of GT treatment (GT d1), showing multifocal opacities in both lungs with foci of consolidation in the upper-left lobe, and f) at day 4 demonstrating resolution of the multifocal opacities with demarked consolidation in the upper left lobe. g) CT-scan two months after treatment demonstrates complete resolution of infiltrates with remaining preexisting small bullae.