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Case Report

First report of severe parainfluenza virus 4B and rhinovirus C coinfection in a liver transplant recipient treated with immunoglobulin

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ABSTRACT

We describe the first reported case of severe pneumonia due to coinfection by parainfluenza virus type 4B and rhinovirus C in a liver transplant recipient. The patient responded promptly to intravenous immunoglobulin and timely infection control measures prevented spreading of the infections. This report highlights respiratory viral coinfections as a possible cause of severe morbidity in transplant recipients and the importance of efficient molecular diagnostic technologies with major impact on clinical practice in a transplant center. It also describes a potential therapeutic strategy for such patients.

1. Why this case is important?

Coinfections by two or more respiratory viruses are increasingly recognized in clinical practice by sensitive molecular diagnostic techniques, especially in pediatric populations [1,2]. However, the clinical significance and impact on disease severity of such coinfections is unclear [2]. We present the first case of severe lower respiratory tract infection due to human parainfluenza (HPIV) 4B, human rhinovirus (HRV) C coinfection in an adult liver transplant recipient, who showed excellent clinical response to intravenous immunoglobulin (IVIG). This case highlights the potential for respiratory viral coinfections to cause severe disease in susceptible patients and also describes the usefulness of IVIG in this setting.

2. Case description

The patient was a 70-year-old man with a background history of type II diabetes mellitus managed with insulin. He suffered from hepatocellular carcinoma (HCC) requiring liver transplantation from a deceased donor in December 2003. He developed cancer recurrence and underwent a second liver transplantation from a deceased donor in July 2012. Unfortunately, reassessment PET-CT 9 months after the second transplantation revealed recurrent HCC in the liver with cervicolumbar bone metastases, progressing despite chemotherapy. In view of treatment refractory terminal malignant disease, all chemotherapy was stopped. The patient was maintained on tacrolimus and sirolimus for post-transplant immunosuppression.

He was admitted in April 2014 with a 1-day history of high fever and productive cough. Chest radiograph on admission showed bilateral lower zone infiltration (Fig. 1a). Leukocyte count was normal (4.21×10^9/L) and lymphocytes were mildly decreased (0.86×10^9/L). He was empirically started on intravenous piperacillin–tazobactam 4.5 g every 8 h for treatment of pneumonia. However, his clinical condition continued to deteriorate with persistent fever and high oxygen requirements; piperacillin–tazobactam was stopped and intravenous meropenem 500 mg every 12 h was commenced.

Abbreviations: HCC, hepatocellular carcinoma; PET-CT, positron emission tomography-computed tomography; RT-PCR, reverse transcription-polymerase chain reaction; IVIG, intravenous immunoglobulin; HPIV, human parainfluenza virus; HRV, human rhinovirus; HSCT, hematopoietic stem cell transplantation.

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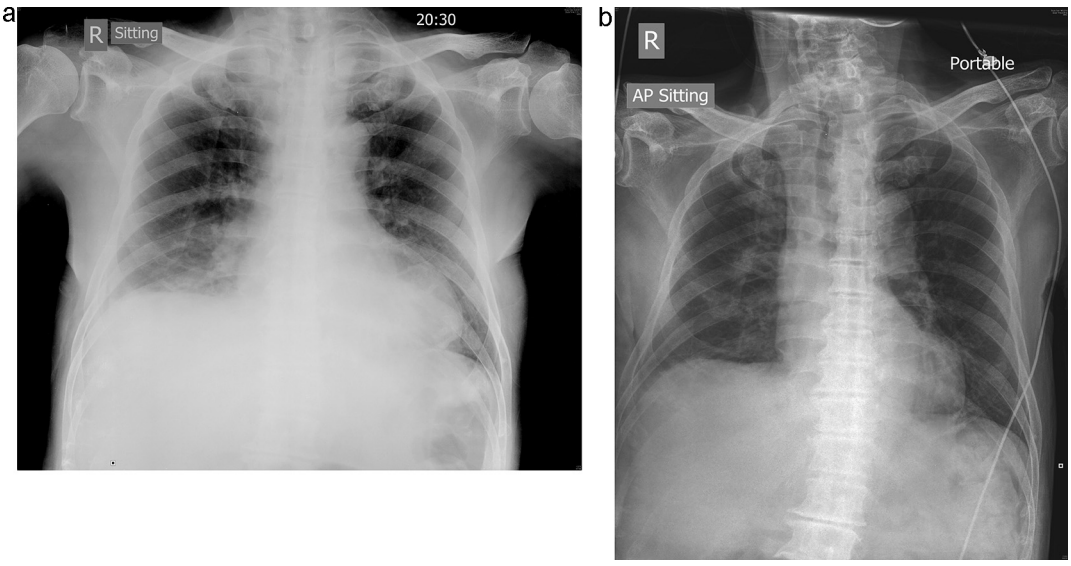

Fig. 1. (a) Chest radiograph of the patient on admission showing bilateral lower zone haziness. (b) Chest radiograph of the patient 2 weeks after discharge showing resolution of the pneumonic changes.

Admission blood culture was negative. Gram stain of the sputum showed many epithelial cells suggestive of heavy oropharyngeal contamination. Culture yielded *Candida albicans* and *Escherichia coli*. In view of the diffuse infiltrative chest radiographic changes, viral pneumonitis was considered in this elderly immunosuppressed patient. Direct immunofluorescence staining (diagnostic hybrids) for influenza A, influenza B, adenovirus, metapneumovirus, parainfluenza-1, 2, 3 and respiratory syncytial virus in the patient's nasopharyngeal aspirate specimen was negative. RT-PCR for *Mycoplasma*, *Chlamydia* and *Legionella* was negative. Cytomegalovirus pp65 antigen in blood leucocytes was negative. Multiplex real-time reverse transcription-polymerase chain reaction (RT-PCR) of RNA extracted from the patient's nasopharyngeal aspirate obtained on admission detected the presence of both parainfluenza type 4 and enterovirus/rhinovirus RNA (C_T values 22.87 and 23.33 respectively). Sequencing of segments of the viral genomes as described in our previous publications followed by phylogenetic analysis enabled definitive identification of the viruses as human parainfluenza virus type 4B (HPIV4B) and human rhinovirus C (HRV-C) as described in our previous studies [3–7] (Fig. 2).

In view of the radiological appearance and the lack of clinical improvement after 5 days of broad-spectrum antibiotics, a diagnosis of HPIV4B and HRV-C coinfection causing pneumonitis was made. The patient was given a single 0.5 g/kg dose of intravenous immunoglobulin (IVIG). The patient was nursed in a side room under standard and droplet precautions. Fever subsided the day after receiving IVIG and the patient could be weaned off supplemental oxygen. The patient was discharged 1 week after receiving IVIG. HPIV4B and HRV-C were no longer detectable in the nasopharyngeal aspirate repeated at discharge. Subsequent chest radiograph obtained 2 weeks after discharge showed resolution of radiological abnormalities (Fig. 1b).

3. Similar and contrasting cases in the literature

To the best of our knowledge, this is the first description of coinfection by HPIV 4B and HRV-C leading to severe disease in an immunocompromised patient. In fact, this is the first reported case of HPIV 4B infection in a liver transplant recipient and also the first reported case of HRV-C infection in a liver transplant recipient. One case report has described a case of fatal coinfection by human metapneumovirus and influenza B in a post-stem cell transplant patient [8].

4. Discussion

We describe the first case of HPIV4B and HRV-C coinfection presenting as a lower respiratory tract infection in an adult liver transplant recipient. He presented acutely with community-acquired pneumonia that did not respond to broad-spectrum antibiotics. A respiratory viral etiology was suspected due to the radiological appearance and non-response to broad-spectrum antibiotics and was confirmed using RT-PCR. Clinical and virological cure was achieved using intravenous immunoglobulin.

HPIV-4 and HRV-C are both respiratory viruses of emerging clinical importance. HPIV-4, a member of the *Rubulavirus* genus of the *Paramyxoviridae* family, is divided into two subtypes – A and B [9]. HRV-C, a member of the *Enterovirus* genus of the family *Picornaviridae*, constitutes a novel rhinovirus species discovered in 2006 [10]. The clinical spectrum of HPIV-4 and HRV-C disease has been difficult to ascertain due to limitations in laboratory detection using conventional diagnostic methods, as both viruses are difficult to isolate from clinical specimens by routine virus culture techniques. Furthermore, commercially available immunofluorescence assay kits for direct detection of respiratory viruses in clinical specimens often do not include monoclonal antibodies against HPIV-4 and HRV-C making routine diagnosis of infections by these respiratory viruses difficult. However, the recent increase in availability of molecular assays has enabled the reliable detection of these viruses in clinical specimens.

In our patient, HPIV-4 and picornaviral RNA was detected in the nasopharyngeal aspirate using a multiplex real-time PCR assay. Sequencing of segments of the viral genomes enabled further typing of the virus isolates as HPIV-4B and HRV-C. This illustrates the importance of state-of-the-art molecular diagnostic technologies to promptly diagnose respiratory viral infections in transplant recipients. The importance of detecting respiratory viruses is sometimes underestimated due to the lack of effective therapeutic options for many of these agents. However, in our patient, the diagnosis enabled the institution of an effective therapy (immunoglobulin). Furthermore, the diagnosis also prompted the timely enforcement of infection control measures to prevent spreading of the infection or even an outbreak in the transplant unit.