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Case Report on the Prevention of an Endemic Outbreak of Influenza B on an Allogeneic Transplant Ward

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Abstract

Respiratory tract infections pose a threat to hematopoietic stem cell recipients, increasing morbidity and mortality rates. To address this, preventive measures are of great importance. We describe the early detection of influenza B in a patient who received a recent hematopoietic transplantation, and elucidation of the transmission path using a point-of-care multiplex polymerase chain reaction panel, leading to prevention of viral spread. The use of risk-score systems and point-of-care testing should be further evaluated.

Introduction

Recipients of hematopoietic stem cell transplantation (HSCT) have a high risk of developing viral respiratory tract infections (RTI). The delay in recovery of lymphocytes, in particular T-lymphocytes [1,2], and the necessity for immunosuppressive medications to attenuate acute graft versus host reaction, raise the risk of developing RTI during the first 100 days after HSCT. Persistent reductions in airflow in patients after HSCT have been shown for common respiratory viruses (CRV) [3]. Moreover, RTI involving the lower respiratory tract are associated with a substantial mortality.

The incidence of viral pneumonia in patients with confirmed viral RTI ranges between 7 and 44% [4–6]. A multi-centre European study reported an influenza-associated mortality of 6.3% in HSCT patients during the influenza A pandemic in 2009 [7]. A seasonal peak can be observed in winter and spring [8]. Other CRV infections, e.g. parainfluenza and respiratory syncytial virus (RSV), also peak seasonally. Preventive strategies and rapid diagnostics are therefore essential, especially during these seasonal peaks.

RTI patients usually present with upper respiratory tract symptoms, such as hoarseness and pharyngitis, congested or runny nose, or coughing [9]. Influenza patients additionally show fever, fatigue, and myalgia. Typical symptoms may be absent, while gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting and diarrhea) may occur [10].

Laboratory diagnostic techniques for detecting CRV include culture, fluorescent antibody staining and molecular testing with real-time reverse transcriptase polymerase chain reactions (RT-PCR). The latter constitutes the current gold standard due to highest specificity and sensitivity [10]. Other PCR-methods may be indicated in certain situations, e.g. quantitative PCR to estimate viral load in cases of viral pneumonia in HSCT patients, or detection of gene variants leading to resistance [10]. Single RT-PCRs for the detection of distinct CRV, and commercial multiplex RT-PCR-systems are now available.

We report on the successful prevention of an influenza B outbreak on a hematologic ward through prompt detection of the infection in a hospitalized allogeneic hematologic stem cell recipient and his spouse.

Case Presentation

In our case report, a 55-year old male patient with chronic myelomonocytic leukemia (CMML-2) was admitted for allogeneic HSCT, six months after initial diagnosis. In his oncological history a neuroendocrine tumor of the ileum was diagnosed and treated by ileac resection and peptide receptor radionuclide therapy eight years earlier. Furthermore, the patient underwent splenectomy and nephrectomy following a traffic accident. Allogeneic HSCT was preceded by 4 cycles of 5-acacytidine. The donor was the patient's human leucocyte antigen-identical (HLA-ident.) daughter. The conditioning regimen consisted of busulfan 8 mg/kg and fludarabin 150 mg/m². Infection prophylaxis included strict hand hygiene, use of face masks and scrub clothing, prophylactic oral application of ciprofloxacin, fluconazole, and acyclovir. Despite this, the patient developed neutropenic fever 3 days before HSCT. *Staphylococcus epidermidis* was cultured in one pair of blood cultures. A computed tomography showed bilateral atypical pneumonia. The antimicrobial regimen was escalated to intravenous piperacillin and tazobactam. Clostridium difficile and clostridium toxins were detected and treated with oral metronidazole. The clinical condition and inflammation parameters abated, and HSCT was performed without further complications.

Sixteen days after HSCT, the patient developed cough, mild yellowish expectoration, and mild dyspnea at exertion. Inflammation parameters increased again and the patient reported fever. Due to progressive dyspnea, a computed tomography of the thorax was performed on day +20 after HSCT. It showed the resolution of the former atypical infiltrates in both lungs. As the reason for the respiratory symptoms remained unclear, on day +21 a Film Array

Respiratory panel was performed from the patient's mouth rinse. With the multiplex RT-PCR Film Array Respiratory Panel (BioFire Diagnostics Inc., Salt Lake City, UT), twenty respiratory pathogens were tested simultaneously, including *Adenovirus, Coronaviruses, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza B, Parainfluenza 1-4, Respiratory Syncytial Virus, Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae*. The test results were available after one hour.

The Film Array panel showed positivity for influenza B. A confirmatory probe was obtained with a RT-PCR [11] to exclude influenza A and with a commercial PCR Kit (LightMix Kit Influenza B Virus, TIB MOLBIOL, Berlin, Germany) for influenza B. Conventional PCR confirmed the presence of influenza B. Oseltamivir was added as antiviral treatment at a dose of 75 mg twice daily for 5 days and the condition resolved along with hematological reconstitution.

To elucidate the infection transmission path, the patient's environment was investigated. The patient's wife had visited him daily during the hospital stay. At the time the patient developed the first symptoms, his spouse had noticed hoarseness without fever or other respiratory symptoms for two days. A sample for Film Array and conventional RT-PCR was obtained from the patient's wife on day 22 and showed positive for influenza B. The patient's spouse refrained from visiting the ward until testing negative for influenza, and no further cases were reported on the ward.

Discussion

This case report demonstrates the impact of diagnosis-time on controlling local outbreaks of CRV. The diagnosis was made within 24 hours using the results of a Film Array Respiratory panel, and the probable transmission path was identified. Influenza B was detected and treated successfully with Oseltamivir despite signs of lower respiratory infection and severe immunosuppression. For both influenza A and B as well as A(H1N1), data from clinical trials suggest that early initiation of effective antiviral treatment reduces progression from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI) to death [12]. This is also true for RSV infections, as antiviral or antibody treatment may be indicated in critical patients [13,14]. For other CRV, although no specific antiviral treatment is currently available [15], rapid diagnosis may assist prevention of further spread of infection. These facts emphasize the benefit of prompt panel diagnostics.

The system used by the medical microbiology department in our hospital provides results on 20 viruses within one hour, using a simple, easy-to-perform method with low hands-on time. Exact pipetting is not required, making peripheral use on an HSCT ward or an emergency department practical. Overall sensitivity is 97% for all tested pathogens with a low failure rate of 1% [16]. The literature gives a specificity of greater than 98% for all tested pathogens [17,18].

The method is expensive, however, and compared to conventional RT-PCR and other automated nested PCR-systems, Film Array has the highest costs per test [16]. Furthermore, simultaneous multiple sample testing with one instrument is not currently possible, requiring multiple instruments for a higher sample throughput. Nonetheless, it should be considered that 20 targets are tested at a time.

Viral infections constitute an important risk factor for patients suffering from hematological malignancies, especially in HSCT patients, with the potential to impact on morbidity and mortality.

Protection of vulnerable patients and rapid detection of infection are crucial steps in the prophylaxis of fatal infections. In cases of confirmed infections, measures to prevent the spread of CRV from one patient to another and to identify transmission paths from external persons should be implemented. Since CRV infections are common in the general population, health care workers (HCW) and family members may act as vectors. The potential to transmit infections through third parties should be especially considered in institutions which transplant patients in an outpatient setting.

While comprehensive data on the testing of caregiving relatives and HCW is lacking, studies have been published on influenza transmission on pediatric wards [19,20]. A prospective study conducted by Melchior et al. [19] in the influenza pandemic 2009, 2010, and 2011 in Brazil, confirmed that asymptomatic influenza infections in HCW and caregivers constitute an issue worthy of consideration in daily routines: Influenza (A, A(H1N1), A nontyped, and B) was detected in 8% of asymptomatic HCW, and 28% of asymptomatic caregivers. Among the vaccinated group, 2.9% and 11.8% tested positive for an influenza subtype contained in the vaccine, respectively [19]. Buchbinder et al. [20] reported on an influenza A(H1N1) outbreak on a pediatric ward, where the source was probably a visiting family member or an asymptomatic HCW. The outbreak led to substantial morbidity in the affected patients. It was successfully limited by strict isolation and hygiene measures, vaccination of all HCW, prophylactic PCR testing and application of Oseltamivir to all patients on the ward [20]. With respect to HCW, a descriptive Mexican study performed between April and September 2009 assayed 83 HCW and 71 patients with symptoms of a respiratory infection. Influenza A(H1N1) was detected in 29, seasonal influenza in 8 HCW. Twenty-six patients were diagnosed with A(H1N1) and 11 with seasonal influenza. Of the patient group, 15 progressed to fatal pneumonia [21].

As general viral testing would be uneconomically, Ferguson et al. [22], suggested a clinical scoring system including signs and symptoms, e.g., stuffed or runny nose, fever, and cough. In this study, the scoring was performed on HSCT patients hospitalized on a hematologic ward. In the case of a score of 2 or more, viral testing was performed with immunofluorescence testing and PCR. The sensitivity and specifity were 62.5% and 56.9.

Conclusions

With the progress in rapid and simple molecular panel diagnostics, assaying of patients, caretakers and HCW with common cold symptoms in high-risk wards should be the subject of further study. As sampling of all patients, visitors and HCWs would be costly, a feasible approach could be the implementation of a clinical scoring system for respiratory symptoms, as suggested anteriorly, and consecutive panel testing with Film Array RP in cases of probable CRV infection. Within one hour individuals positive for CRV could be isolated and, if indicated and available, obtain premature specific treatment. This approach could potentially reduce the morbidity and mortality in this high-risk patient population and shorten the stay on intensive care units. The use of antibiotics and antimycotics for superinfection with bacteria and molds, (e.g. *Staphylococcus aureus* [23] and *Aspergillus fumigatus*) is frequent, and considering this, the implementation of HCW-testing in high-risk wards may lead to economic benefits. Moreover, such an approach could increase awareness of preventive measures and could thereby even have an impact on vaccination rates against Influenza.

Consent

Written informed consent for this publication was given by the patient in presence of his spouse.

Authors' Contributions

KH and JS interpreted the material and wrote the manuscript. MB, JS, ÄB and FS planned the diagnostic approach, monitored the clinical course and treated the patient and his wife. FG introduced the PCR-based panel diagnostic at our clinic and conducted confirmatory viral testing. All authors reviewed and approved the final manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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