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Case report

BK papova virus pneumonia following hematopoietic stem cell transplantation

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Summary:

BK papova virus infection is frequently seen after bone marrow transplantation as a causative agent of hemorrhagic cystitis. We report an 8-month-old child with osteopetrosis who died of a severe interstitial pneumonia after receiving an unrelated umbilical cord transplant. On autopsy, BK virus was detected in the lung tissue using immunofluorescence assay, cell culture and PCR. No other pathogens were recovered. BK virus infection should be considered as a cause of interstitial pneumonia in children undergoing transplantation.
Keywords: BK virus; interstitial pneumonia; bone marrow transplantation

Opportunistic infection is a frequent complication of bone marrow transplantation and is associated with significant morbidity and mortality, including severe interstitial pneumonia.[1] Many infectious agents have been implicated in the development of interstitial pneumonia including bacteria, fungi, toxoplasma, *Pneumocystis carinii*, and various viruses.[2,3] BK virus infection is frequently seen in the bone marrow transplant setting as a causative agent of hemorrhagic cystitis and rarely as a cause of hepatitis.[4,5] These infections are thought to result from reactivation of latent viral infection.[6] There are no prior reports of BK virus-associated interstitial pneumonia in a post-transplant patient.

We report a child who underwent hematopoietic stem cell transplantation using an unrelated umbilical cord blood unit who developed severe interstitial pneumonia and adult respiratory distress syndrome (ARDS). The patient succumbed to pneumonia and on autopsy BK virus was found in her lungs in the absence of other pathogens. To our knowledge, this represents the first reported case of BK virus-associated pneumonia in a bone marrow transplant patient.

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Case report

An 8-month-old girl was referred for bone marrow transplant as treatment for osteopetrosis. No HLA-identical family members were available, and a 5 month search of the volunteer donor registries failed to find an appropriate donor. Further searches identified an unrelated umbilical cord blood unit which was a 4 of 6 match with a 1-antigen mismatch at the A locus and a 1-antigen mismatch at the B locus. By high resolution DNA typing this unit was DRB1 identical. At the time of admission the patient was clinically well and had no evidence of infection. She received busulfan (640 mg/m^2), cyclophosphamide (200 mg/kg) and antithymocyte globulin (90 mg/kg) as preparation for the transplant. GVHD prophylaxis included a combination of cyclosporine and prednisone. Infection prophylaxis consisted of intravenous acyclovir (1500 mg/m^2/day), amphotericin (0.3 mg/kg/day), i.v. pentamidine monthly, and immunoglobulin 500 mg/kg weekly.

The child developed fever on day −7 and was started on vancomycin and amikacin. The fever resolved and bacterial cultures remained negative. On day −6 she developed rhinorrhea and tachypnea. A nasopharyngeal specimen was submitted for viral culture and direct examination for the presence of major respiratory viruses including adenovirus, respiratory syncytial virus, parainfluenza viruses types 1, 2 and 3, influenza virus types A and B, and cytomegalovirus. No viruses were detected. Chest roentgenogram revealed no evidence of infiltrate. The patient continued to have tachypnea but was afebrile and clinically well until day −3 when she developed fever, increasing tachypnea, hypoxia and hypercapnia. Repeat chest roentgenogram revealed a diffuse interstitial infiltrate. The patient was transferred to the pediatric intensive care unit and begun on mechanical ventilation. At the time of intubation, a tracheal aspirate sample was sent. This sample was subsequently found to contain BK virus.

Because of the abnormal airway in this patient with osteopetrosis, bronchoscopy could not be performed. She was started on daily IVIG (1 g/kg/day) as well as amphotericin (1 mg/kg/day) and imipenem. She developed hemorrhagic cystitis on day +3. This was controlled with increased hydration. Urine cultures for bacterial and fungal pathogens were negative. Viral culture of the urine was positive for BK virus. Although her respiratory status

remained stable for several days, on day +17 she developed hypotension requiring pressor support, renal failure requiring continuous veno-venous hemofiltration, and worsening pulmonary disease requiring increasing ventilatory support. She was placed on high frequency ventilation, but her respiratory status continued to deteriorate as did her renal function. On day +19, with continued worsening of her respiratory status despite maximal support, the patient died. On autopsy, she had severe diffuse alveolar damage, and early fibrosis. Although no bacteria or fungi were recovered from autopsy tissues, BK virus was isolated from cell cultures of the lung tissue and bladder.

The identification of the virus was based on the detection of viral antigens in human neonatal kidney (HNK) cell culture (Biowhittaker, Walkersville, MD, USA), using an immunofluorescence assay. A mouse monoclonal antibody (IgG2A) (Chemicon International, Temecula, CA, USA) directed against the large T antigen of the BK virus was used as the primary antibody in the assay. The specificity of the monoclonal antibody was confirmed by testing the reagent for appropriate responses to both a HNK culture inoculated with an identified strain of BK virus (No. VR-837; American Type Culture Collection, Rockville, MD, USA), and uninoculated HNK cells. The specimens were also screened for the presence of the more common respiratory viruses using an immunofluorescence assay (Bartels, Issaquah, WA, USA). No RSV, parainfluenza types 1–3, adenovirus or influenza A/B were detected. The presence of BK virus was confirmed in both the autopsy lung tissue and cell culture using a polymerase chain reaction (PCR) utilizing specific BK primers originally described by Jin *et al*.[7] These primers were previously shown to be specific for amplification of BK virus sequences.

Discussion

BK virus, a polyomavirus, commonly occurs in the general population. In some series, over 80% of adults are seropositive.[8] After primary infection, the virus remains latent in the kidney and possibly in lymphocytes.[9] Reactivation of BK virus resulting in clinical disease can occur during periods of severe immunosuppression. The virus has been isolated from the urine of up to 50% of patients undergoing BMT, and this reactivation has been implicated in the development of hemorrhagic cystitis after transplant.[10] In one recent study, hemorrhagic cystitis occurred in 25% of patients transplanted with a cyclophosphamide containing regimen.[4] More than half of these patients were positive for BK virus. BK virus has also been implicated as a causative agent of hepatitis following marrow transplantation.[11]

Why this patient developed interstitial pneumonia with BK virus is unclear. Although many viruses have been implicated as causing interstitial pneumonia in patients undergoing bone marrow transplantation, BK virus has not been previously reported. Although usually asymptomatic, primary infection is thought to occur at a young age and by the respiratory route.[6,12] After an initial primary infection, the virus remains latent in the kidney and can reactivate when T cell function is deficient.[6] The fact that this patient developed hemorrhagic cystitis and BK virus was identified in the urine further supports the role of BK virus in this patient's illness. The lack of previously documented pulmonary infection due to this pathogen may be attributed to the difficulties isolating the virus from clinical specimens coupled with the lack of widely available immunodiagnostic reagents for the detection and identification of BK viral antigens in cell culture. Alternatively, the early onset of disease in our patient prior to severe immunosuppression and her age of 8 months suggests that she may have developed primary infection with BK virus coincident with her hospital admission. As her immunodeficiency progressed following conditioning chemotherapy, she developed severe pneumonia. This would clearly explain the early onset of symptoms during the transplant process. Furthermore, this patient also had a compromised airway secondary to her underlying disease which may have also contributed to the severity of her illness.

There is no specific therapy for BK virus infection. The mainstay of therapy for BK virus-associated hemorrhagic cystitis is management of symptoms until recovery of immunologic function. There is one case report suggesting the efficacy of vidarabine.[13]

This report describes for the first time a patient undergoing bone marrow transplantation who developed diffuse interstitial pneumonitis and subsequently adult respiratory distress syndrome attributed to BK virus. BK virus infection should be considered as a possible cause of interstitial pneumonitis in the pediatric bone marrow transplant patient.

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