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Case report

Pneumonitis post-haematopoeitic stem cell transplant – Cytopathology clinches diagnosis

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ABSTRACT

Background: Primary BK virus (BKV) infection is probably acquired by the respiratory route in childhood, and latent virus persists principally in the urinary tract. BKV reactivation is implicated in late onset haemorrhagic cystitis (HC) post Haematopoietic Stem Cell Transplant (HSCT). There is emerging evidence that BKV can cause life-threatening pneumonitis in immunocompromised individuals.
Objectives: To describe the first known case of BKV pneumonitis in an adult HSCT recipient.
Study design/Results: A 19-year old male underwent an ABO–incompatible, volunteer unrelated donor allogeneic HSCT for high risk AML. The post-transplant period was complicated by moderate-severe cutaneous and gut acute graft-versus-host disease (aGVHD) and severe HC, attributable to BKV. Treatment encompassed intensification of immunosupression for aGVHD and weekly intravenous (IV) cidofovir (2.5 mg/Kg) for BK viruria.

He was readmitted with presumed septic shock and acute renal failure. After a transient improvement on broad spectrum antibacterials, he suffered significant respiratory deterioration. CT imaging revealed diffuse 'ground-glass' attenuation. Cytopathological assessment of a broncho-alveolar sample (BAL) was consistent with polyomavirus pneumonitis. No other cause was found to account for the respiratory deterioration. He did not respond to therapy and died of multi-organ failure.
Conclusions: BKV is implicated in haemorrhagic cystitis in HSCT recipients but not routinely considered as a cause of pneumonitis. There are just 5 other cases in the literature, including 3 patients with AIDS. BKV should be considered as a possible cause of pneumonitis in HSCT recipients.

1. Why this case is important

That BK virus (BKV) can cause life-threatening pneumonitis in immunocompromised individuals has been shown in a small number of post-mortem case reports.[1–5] Here we report the first case of BKV pneumonitis in an adult haematopoietic stem cell transplant (HSCT) recipient and the first to be diagnosed antemortem by cytopathological examination of bronchoalveolar lavage fluid (BAL).

2. Case description

A 19-year old male was diagnosed with poor risk acute myeloid leukaemia (AML), due to the presence of complex cytogenetic abnormalities. After failure of initial treatment (daunorubicin, cytarabine arabinoside, etoposide and immunoconjugate drug gemtuzumab ozogamicin), the fludarabine, cytarabine arabinoside, granulocyte colony stimulating factor (GCSF) and idarubicin (FLAG-Ida) regimen resulted in complete cytogenetic remission. The initial clinical course was complicated by cardiac impairment secondary to anthracyline exposure, significant gastrointestinal bleeding due to chemotherapy-induced thrombocytopenia and presumed pulmonary fungal disease. Nonetheless, he recovered well with appropriate antimicrobial and supportive therapy and received a further course of FLAG consolidation prior to transplantation. He underwent a one-antigen mismatched unrelated donor HSCT, with minor ABO blood group incompatibility. Both donor and recipient were CMV seropositive. He had myeloablative conditioning

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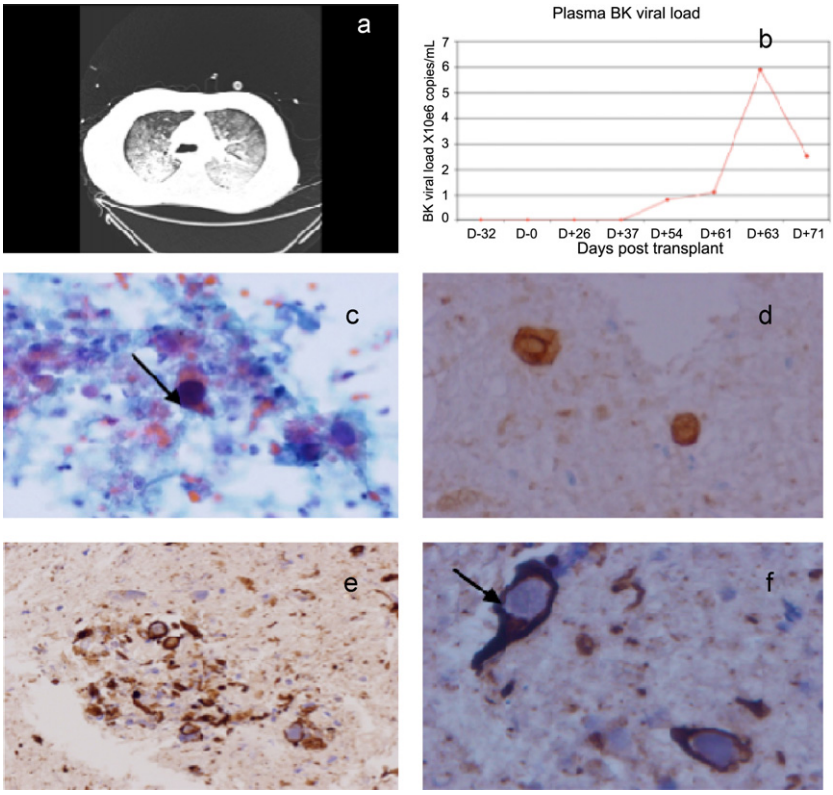

Fig. 1. (a) Selected CT image of lung demonstrating diffuse ground glass opacification and consolidation; (b) plasma BK virus levels in copies/mL × 10^6; (c) H&E stain of BAL showing enlarged cell which contains a large intranuclear basophilic viral inclusion body similar to that seen in renal tubular epithelial cells in BK nephropathy; (d) SV40 immunohistochemistry on cell block prepared from washings with 'brown dots' depicting nuclei with viral inclusions thereby confirming polyoma virus infection; (e) immunohistochemistry (MNF-116 positive) confirming epithelial nature of cells; and (f): high power view of (e) – the brown stain is MNF-116. Viral inclusions are seen within these epithelial cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

with oral busulphan (16 mg/kg) and high dose cyclophosphamide (60 mg/kg), and T-cell depletion with alemtuzumab (100 mg). Antimicrobial prophylaxis included ciprofloxacin, posaconazole, aciclovir, pentamidine nebulizers and isoniazid.

The early post-transplant period was complicated by grade IV acute graft-*versus*-host disease (aGVHD) involving the skin and gut. He subsequently developed grade 4 haemorrhagic cystitis (HC) at day +30 post-HSCT, associated with BKV loads of >9 million copies/mL (log 9.60) in urine and 5000 copies/mL in plasma. Intensification of immunosuppression for worsening aGVHD included 2 mg/kg methylprednisolone and weekly intravenous (IV) cidofovir (1 mg/kg)[6] was commenced for ongoing BKV-related HC.

Despite treatment response facilitating discharge, he was readmitted on day +63 with presumed non-neutropenic sepsis and acute renal failure requiring endotracheal intubation and inotropic support. Empiric broad spectrum antimicrobial therapy covered the subsequent diagnoses of *Pseudomonas aeruginosa* Hickman line infection and *Escherichia coli* urosepsis. At this time the plasma BKV was >1 million copies/mL with a persistent urine BKV load of >9 million copies/mL. The situation improved transiently, with extubation and cessation of inotropes when he suffered significant respiratory deterioration requiring augmented inotropic and respiratory support. Subsequent fine slice CT pulmonary imaging revealed the presence of diffuse 'ground-glass' attenuation (Fig. 1a) and BAL was performed. Antimicrobial therapy was extended to include treatment dose IV ganciclovir, liposomal amphotericin and co-trimoxazole but all bacterial cultures remained negative. He also received replacement dose immunoglobulin therapy. Whilst CMV DNA remained undetectable in blood, the plasma BKV load continued to rise to 5 million copies/mL (Fig. 1b) with persistent grade 4 HC. Intravenous cidofovir was increased to 5 mg/kg/week (adjusting for renal impairment) with addition of probenecid cover and concurrent intravesicular cidofovir.[7] Unexpectedly, cells with a striking resemblance to urine decoy cells were seen on cytopathological examination of the BAL specimen (Fig. 1c–f). Immunohistochemistry with pan-cytokeratin antibody, MNF-116 (Dako) confirmed these to be of epithelial origin. The positive stain for SV40 (Calbiochem®) confirmed polyoma virus infection attributable to BKV. No other cause was found to account for the respiratory deterioration. Unfortunately, the patient did not respond to ongoing aggressive therapy and died with multi-organ failure 2 weeks later. An autopsy was not performed.

3. Other similar and contrasting cases in the literature

Only 5 cases of BK virus interstitial pneumonitis have been previously reported in the literature, and all were diagnosed post-mortem[1–5] as summarized in Table 1.

4. Discussion

BKV, JC virus and simian Virus 40 (SV40) are non-enveloped polyoma DNA viruses of the papovaviridae family sharing 70–75% genetic homology.[8] Primary BKV infection is probably acquired by the respiratory route at a median age of 4–5 years, and latent virus persists principally in the urinary tract.[8] Infection is widespread with adult seroprevalence of 46–94% worldwide.[8] Both primary infection and subsequent reactivations are subclinical, but BKV reactivation is implicated in late onset HC post HSCT in