BK virus pneumonia following stem cell transplantation against diffuse large B-cell lymphoma

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Keywords
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Abstract
The patient, a 70-year-old woman with diffuse large B-cell lymphoma (DLBCL), developed haemorrhagic cystitis associated with the BK virus (BKV) and adenovirus type 11. Moreover, chest computed tomography showed ground-glass opacity (GGO) in the bilateral upper lobe, and we performed bronchoalveolar lavage (BAL). The BKV DNA load was elevated not only in blood but also in BAL fluid (BALF), leading to the diagnosis of BKV pneumonia. After administering cidofovir, the respiratory symptoms and GGO abated. Therefore, detection of BKV DNA in BALF is useful for diagnosing BKV pneumonia.

Introduction
The BK virus (BKV) often causes nephropathy in immunocompromised patients but rarely causes pneumonia [1,2]. BK virus pneumonia has been reported most often in children or in acquired immunodeficiency syndrome patients. It is difficult to diagnose BKV pneumonia, which is a rare, fatal disease. Here, we report the case of a patient who developed BKV pneumonia after autologous peripheral blood stem cell transplantation (auto-PBSCT) against relapsed diffuse large B-cell lymphoma (DLBCL). The patient was diagnosed with BKV pneumonia by bronchoalveolar lavage (BAL), and the symptoms improved after administration of cidofovir. Therefore, performing BAL proved useful for diagnosing BKV pneumonia.

Case Report
A 70-year-old woman was diagnosed with DLBCL (Ann Arbor Stage: IIIA) and received chemotherapy but relapsed. She was admitted to our hospital in 2017 to undergo auto-PBSCT after salvage chemotherapy. She suddenly developed grade 3 haematuria on the day of transplantation. We detected a BKV DNA load of $5.0 \times 10^7$ copies/mL and adenovirus (ADV) type 11 DNA load of $5.0 \times 10^7$ copies/mL in the urine and diagnosed her with haemorrhagic cystitis (HC) associated with BKV and ADV. Although she received immunoglobulin and adenine arabinoside, the HC symptoms did not improve. Moreover, we detected a BKV DNA load of $2.2 \times 10^2$ copies/mL in the blood and diagnosed the patient with BKV viraemia with complications. Although we administered cidofovir (1 mg/kg, three times a week) from days 8 to 26 post-auto-PBSCT, the HC symptoms persisted. The ADV DNA load in urine became negative, but the BKV DNA load in urine did not decrease. Overall, the BKV infection did not stabilize adequately.

She exhibited respiratory failure and elevated serum C-reactive protein levels at day 32 (Table 1). Chest computed tomography (CT) showed ground-glass opacity (GGO) in the bilateral upper lobe, and we performed BAL at day 34. Although BAL fluid (BALF) was not macroscopically reddish, BAL slightly detected red blood cells on cytology. In BALF, the BKV DNA load was $1.5 \times 10^2$ copies/mL, although the ADV and cytomegalovirus DNA loads were not elevated. Although we could not perform lung biopsy because the blood platelet count was low, we diagnosed the patient with BKV pneumonia by bronchoalveolar lavage (BAL). The detection of BKV DNA in BALF is useful for diagnosing BKV pneumonia.
pneumonia. After re-administering cidofovir, respiratory symp-
toms and GGO in CT abated, although HC symptoms per-
sisted (Fig. 1). The patient has not experienced a relapse of
BKV pneumonia and DLBCL even after 11 months.

Discussion

In this study, the patient underwent auto-PBSCT after sal-
vage chemotherapy against DLBCL. She developed pneu-
monia during treatment of BKV infection and was diagnosed
with BKV pneumonia following detection of BKV DNA in
BALF. Therefore, the detection of BKV DNA in BALF is
useful for diagnosing BKV pneumonia.

Table 1. Laboratory Data of the Patient at the Onset of Pneumonia

| Biochemistry     | Serology         | Uralysis          |
|------------------|------------------|-------------------|
| TP 5.8 g/dL      | KL-6 249 IU/mL   | SG 1.007          |
| Alb 3.1 g/dL     | SP-A 84.6 ng/mL  | pH 7.0            |
| AST 31 IU/L      | SP-D 58.6 ng/mL  | Uric protein (+)  |
| ALT 13 IU/L      | BNP 70 pg/mL     | Uric protein (+)  |
| LDH 224 IU/L     | β-D Glucan 10 pg/mL | Uric sugar (−) |
| T-Bil 0.3 mg/dL  | IgG 402 mg/dL    | Bil (−)           |
| BUN 24 mg/dL     | IgA 32 mg/dL     | RBC >100/HPF      |
| Cre 1.04 mg/dL   | IgM 15 mg/dL     | WBC 1–4/HPF       |
| Na 5.1 mg/dL     | Procalcitonin 0.17 ng/mL | PCR in urine |
| Cl 136 mEq/L     | <1.0 EU          | BKV DNA >5.0 × 10⁵ copies/mL |
| K 100 mEq/L      | PR3-ANCA <1.0 EU | ADV DNA 2.2 × 10⁵ copies/mL |
| CRP 4.5 mEq/L    | siL-2R 2270 IU/mL | BALF (Lt, B3b) |
| Haematology      | Anti MAC Ab (−)  | Total cell count 3.4 × 10⁵/mL |
| WBC 6170 /μL     | C7HRP (−)        | Macrophage 76%    |
| Neut. 58.3%      | Aspergillus Ag 0.1 | Neut. 8%         |
| Lymp. 21.4%      | Candida Ag <0.02 | Lymp. 16%        |
| Mono. 19.0%      | Cryptococcosis Ag (−) | CD4/8 ratio 1.08% |
| Eos. 1.1%        | PCR in blood     | PCR in BALF       |
| RBC 259 × 10⁵/μL | BKV DNA 2.4 × 10⁴ copies/mL | BKV DNA 1.5 × 10² copies/mL |
| Hb 8.3 g/dL      | ADV DNA <1.0 × 10² copies/mL | ADV DNA (−) |
| Hct 25.6%        | ADV DNA (−)      | CMV DNA (−)       |
| MCV 98.8 fl      | Pneumocystis jirovecii DNA (−) |
| MCH 32 pg        | Plt 6.0 × 10⁴/μL |

The BKV, JC virus, and simian virus 40 belong to the
non-enveloped polyoma DNA viruses of the human
polyomavirus family [1]. The BKV mostly infects the
respiratory route during childhood and remains latent in
the renal tubule and urothelial cells. In immunocompro-
mised individuals, such as patients with acquired immu-
nodeficiency syndrome and transplant recipients who are
undergoing immunosuppressive therapy, BKV reactivates
and most often causes nephropathy; BKV nephropathy
occurs in up to 8% of the adult recipients of kidney allo-
grafts and causes renal dysfunction [1]. Due to reacti-
vated BKV spreading through the blood, in addition to
nephropathy, BKV causes ureteric stenosis, HC, and pneu-
monia in a small number of cases [2]. Although there is no
standard therapeutic agent against BKV infection, cidofovir is one of the effective drugs.

One of the forms of BKV infection, BKV pneumonia is a rare fatal disease that is difficult to diagnose. It is necessary to perform biopsy for a definitive diagnosis of BKV infection. However, thrombocytopenia induced by chemotherapy makes the diagnosis of BKV infection difficult. There was no patient who exhibited improvement of symptoms in the previous six case reports [3]. This is the first case, however, where BKV pneumonia was diagnosed during life and improved by cidofovir administration.

The detection of BKV DNA in the urine and plasma is a useful non-invasive approach for the diagnosis of BKV infection [1]. In both immunocompetent and immunocompromised adult patients, BKV is primarily detected in the blood and urine and is not at all detected in BALF [4], and in a previous report, BKV pneumonia was diagnosed based on the positive BKV DNA-polymerase chain reaction (PCR) results for BALF [3]. Therefore, the detection of BKV DNA in BALF should be useful for diagnosing BKV pneumonia.

In the present case, the patient exhibited pneumonia with elevated plasma BKV DNA load after receiving chemotherapy against DLBCL. We did not perform lung biopsy, and the BKV DNA-PCR results might have been positive due to contamination of blood. However, we detected an elevated BKV DNA load in BALF and the patient’s respiratory symptoms, and the GGO observed in CT abated after re-administering cidofovir. Therefore, we diagnosed the patient with BKV pneumonia.

It is unclear as to why the symptoms of BKV pneumonia improved, although the HC symptoms did not improve after re-administrating cidofovir. The BKV DNA load in urine was much higher than in BALF. The response to cidofovir might be different between HC and pneumonia because the cidofovir treatment period for BKV infection has been reported to be significantly associated with BKV DNA load [5].

Although BKV pneumonia is fatal, it is possible to improve the symptoms if the patients are treated early, as in the present case. It should be noted that we performed BAL and detected BKV DNA in BALF as soon as respiratory failure and elevated plasma BKV DNA load were detected. In conclusion, in this study, the patient underwent auto-PBSCT after salvage chemotherapy against DLBCL. She developed pneumonia during treatment of BKV infection and was diagnosed with BKV pneumonia following detection of BKV DNA in BALF. Therefore, the detection of BKV DNA in BALF is useful for diagnosing BKV pneumonia.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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