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Case Report

Disseminated adenovirus infection in a patient with relapsed refractory multiple myeloma undergoing autologous stem cell transplantation and pomalidomide/dexamethasone as salvage regimens☆

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ABSTRACT

Background: Disseminated adenovirus (ADV) infection is a fatal complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT), however, it is rare following autologous peripheral blood stem cell transplantation (auto-PBSCT) or chemotherapy alone.
Case: A 66-year-old Japanese female with relapsed and refractory multiple myeloma (RRMM) received auto-PBSCT, achieving partial response. To obtain a greater response, pomalidomide/dexamethasone was started on day 28 after auto-PBSCT, but was stopped on day 41 due to thrombocytopenia, fever, and gross hematuria. Additionally, she complained of abdominal pain on day 46. Blood tests revealed elevation of transaminases and alkaline phosphatase. There was no evidence of bacterial or fungal infections or progression of MM. ADV titer in urine and serum were 3.41×10^5 copies/mL and 6.76×10^3 copies/mL, respectively. CT scans revealed cystitis, urethritis, and peritonitis. Since more than two organs were infected with ADV, she was diagnosed with disseminated ADV disease. After 5 weeks of supportive care, all symptoms resolved. ADV titer decreased to 5.90×10^2 copies/mL in urine and became negative in serum on day 80. However, she succumbed to the MM a little more than a month later.
Conclusion: Disseminated ADV infection can occur even in non-allogeneic transplant settings, such as in severely immunocompromised patients with MM who receive auto-PBSCT and repeated salvage therapies. Although it is a rare event, the mortality rate of this disease is very high, and hence, early diagnosis and interventions are needed in suspected cases.

1. Introduction

Adenoviruses are common viruses that infect the eyes, airways and lungs, intestines, urinary tract, and nervous system. Although the infections usually cause only mild symptoms in immunocompetent individuals, they can be serious in patients with

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immunodeficiency, especially in allo-HSCT recipients.[1] ADV-HC[2] is a frequent complication of allo-HSCT. Supportive therapies, including fluid therapy, blood transfusion, immunoglobulin supplements, and reduction of immunosuppressants, and anti-viral therapy, such as CDV[3] and RIV,[4] are the main treatments of ADV-HC. However, the infection occasionally progresses to ADV viremia and disseminated disease. Disseminated ADV infection is potentially fatal, around 60% mortality rate in allo-HSCT recipients [1].

Chemotherapy alone or auto-PBSCT[5] can also cause ADV-HC in rare cases. However, these therapies seldom cause disseminated ADV infection because chemotherapy or auto-PBSCT-induced immunosuppression is usually transient and milder than that after allo-HSCT.

POM[6] is a new agent for BOR[7]/LEN[8]-resistant MM,[9] and has more potent antitumor effects than previously used IMiDs[10] [2]. We herein report a patient with relapsed refractory MM who developed HC with ADV dissemination after auto-PBSCT followed by POM/DEX.[11]

2. Case report

A 66-year-old Japanese female presented to our hospital with lumbago. MRI[12] revealed a vertebral tumor (6.5 × 5.0cm). Pathological examination of the biopsy specimen revealed plasmacytoma. Without evidence of systemic disease throughout the evaluation, she was diagnosed with solitary plasmacytoma of the bone, IgG-kappa type, and was treated with localized irradiation of the vertebral tumor, achieving CR.[13] However, tumors reappeared in her left humerus and mandibular bone at seven months after diagnosis. Disease progression to symptomatic MM was diagnosed. She was treated with CBD (CPM[14] 400 mg/body, BOR 1.3 mg/m^2, DEX 40 mg on days 1, 8, 15, and 22 of each 28-day cycle) and localized irradiation, achieving CR. However, a tumor subsequently reappeared in her left axillary region. CBD was switched to LEN/DEX (LEN 4 mg on days 1–21, DEX 40 mg on days 1, 8, 15, and 22 of each 28-day cycle). Although the left axillary tumor disappeared, a tumor reappeared in her right breast. Considering the chemotherapy resistance and no signs of plasma cell infiltration in bone marrow or peripheral blood, high dose chemotherapy followed by auto-PBSCT was planned for better disease control. After receiving adequate explanations regarding the risks and benefits, she gave consent for auto-PBSCT. Fifteen months after diagnosis, she received high-dose CPM followed by auto-PBSCH,[15] yielding an adequate number of CD34-positive cells (8.68 × 10^6 cells/kg). The tumor size was temporarily reduced, but regrowth within two weeks. Salvage VCAP therapy (Vincristine 1 mg/body on day 1, CPM 100 mg/body on days 1–4, doxorubicin 25 mg/m^2 on day 1, prednisolone 60 mg/m^2 on days 1–4 of each 21-day cycle) was ineffective. Two months after auto-PBSCH, she received high-dose melphalan (200 mg/m^2), followed by auto-PBSCT using 4.34 × 10^6/kg of CD34-positive cells, which resulted in a PR.[16]

On day 28 after auto-PBSCT (laboratory data shown in Table 1), POM/DEX (POM 4 mg on days 1–21, DEX 20 mg on days 1, 8, 15, and 22) was started. On day 36, she complained of frequent urination and high grade fever (Fig. 1). She was diagnosed with a UTI[17] due to ESBL[18] producing *Escherichia coli*, and MEPM[19] was started. Although the fever initially diminished, high grade fever reappeared. Empiric antibiotic therapy with VCM[20], LVFX,[21] and MINO[22] alleviated the fever. On day 38, gross hematuria appeared. Since POM-induced thrombocytopenia might contribute to hematuria, POM/DEX was stopped on day 40. Subsequently, her transaminase and alkaline phosphatase gradually increased and she complained of high fever and left abdominal pain on day 46. Blood and urine culture were negative, and empiric antibiotics and antifungal therapy were ineffective. Urine cytology showed no evidence of malignancy. CT[23] scans indicated cystitis, ureteritis, and peritonitis (Fig. 2). Since urine ADV titers were 3.40 × 10^5 copies/mL, she was diagnosed with ADV-HC. We assumed that inflammation due to ADV-HC had spread to the left retroperitoneal space, leading to peritonitis. Hence, we continued supportive therapies, including fluid therapy, blood transfusion, and immunoglobulin supplementation. We also switched antiviral therapy from acyclovir to ganciclovir to treat CMV[24] viremia, although it was ineffective in treating the ADV infection. Her serum ADV titer was 6.80 × 10^3 copies/mL. In addition to ADV viremia, cystitis, ureteritis, and peritonitis, she also seemed to have developed liver dysfunction secondary to ADV infection, although the possibility of drug-induced toxicity remained. In accordance with European guidelines for the diagnosis and treatment of ADV infection in leukemia and stem cell transplantation [3], the cystitis, ureteritis, peritonitis, and liver dysfunction were considered as “probable ADV disease”. Since more than two organs seemed to be infected with ADV, she was diagnosed with disseminated ADV disease. Four weeks after stopping POM/DEX, her symptoms gradually improved. On day 78 after auto-PBSCT, CT scans showed improvement of cystitis and ureteritis, and ADV titer decreased to 5.90 × 10^2 copies/mL in urine and became negative in serum on day 80. Although she recovered from disseminated ADV infection, the size of the breast tumor increased again and a tumor appeared on the left side of her abdomen. Relapsed myeloma was diagnosed, and POM/DEX was resumed with dose reduction of POM to 2 mg. However, soon after resuming POM/DEX, gross hematuria reappeared, and POM/DEX was discontinued. Subsequently, her abdominal tumor enlarged and she received local irradiation to relieve her symptoms. Although her hematuria was resolved, she developed plasma cell leukemia and died due to disease progression on day 126.

3. Discussion

ADV infection usually cause mild and transient symptoms in immunocompetent patients, however, in immunocompromised patients, ADV may cause disseminated disease, which are sometimes fatal [4]. Disseminated ADV infection is defined as the

[1] Allo-HSCT, allogeneic hematopoietic stem cell transplantation.
[2] ADV-HC, Adenovirus-associated hemorrhagic cystitis.
[3] CDV, cidofovir.
[4] RIV, ribavirin.
[5] Auto-PBSCT, autologous peripheral blood stem cell transplantation.
[6] POM, pomalidomide.
[7] BOR, bortezomib.
[8] LEN, lenalidomide.
[9] MM, multiple myeloma.
[10] IMiDs, immunomodulatory drugs.
[11] POM/DEX, pomalidomide with low-dose dexamethasone therapy.
[12] MRI, magnetic resonance imaging.
[13] CR, complete response.
[14] CPM, cyclophosphamide.
[15] Auto-PBSCH, autologous peripheral blood stem cell harvesting.
[16] PR, partial response.
[17] UTI, urinary tract infection.
[18] ESBL, extended-spectrum beta lactamase.
[19] MEPM, meropenem.
[20] VCM, vancomycin.
[21] LVFX, levofloxacin.
[22] MINO, minocycline
[23] CT, computed tomography.
[24] CMV, cytomegalovirus.

Table 1
Laboratory data at starting pomalidomide/dexamethasone.

Complete blood count		Blood chemistry			
WBC	7500/μL	TP	6.5 g/dL	LDH	297 U/L
Myelo	0.5%	Alb	3.1 g/dL	ALP	35 U/L
Meta	0.5%	UN	21 mg/dL	Glu	112 mg/dL
Stab	8.0%	Cre	0.58 mg/dL	CRP	0.56 mg/dL
Seg	61.0%	UA	3.3 mg/dL	IgG	1438 mg/dL
Lym	18.0%	T-Bil	0.3 mg/dL	IgA	282 mg/dL
Mono	12.0%	Na	142 mEq/L	IgM	35 mg/dL
Hb	7.3 g/dL	K	3.9 mEq/L	Free κ	<0.6 mg/dL
MCV	97 fL	Cl	109 mEq/L	Free λ	<0.6 mg/dL
MCH	32.6%	Ca	9.1 mg/dL	HBs antigen/antibody	negative/negative
MCHC	33.6%	IP	3.4 mg/dL	HCV antibody	negative
ret	59‰	AST	27 U/L	βD glucan	<3.9 pg/mL
Plt	13.2 × 10^4/μL	ALT	55 U/L	D-Dimer	4.0 μg/mL

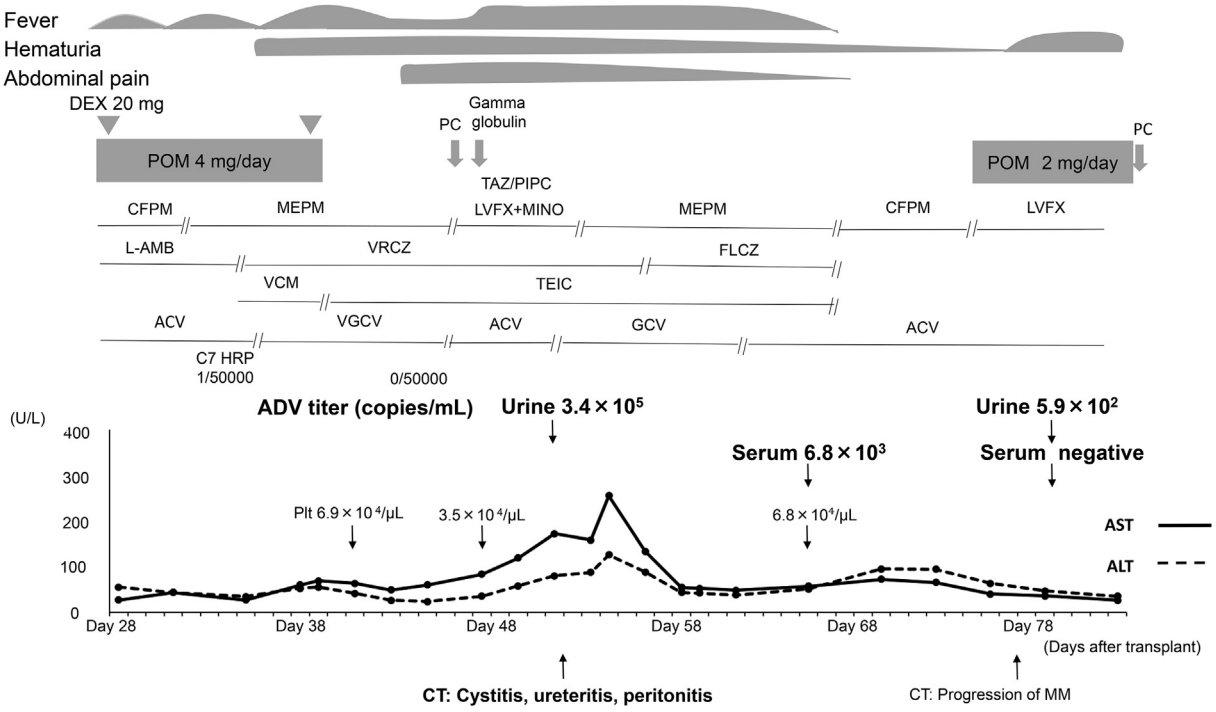

Fig. 1. Clinical course after starting POM/DEX. ACV, Acyclovir; ADV, Adenovirus; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; CFPM, Cefepime; CT, Computed tomography; DEX, Dexamethasone; FLCZ, Fluconazole; GCV, Ganciclovir; L-AMB, Liposomal Amphotericin B; LVFX, Levofloxacin; MEPM, Meropenem; MINO, Minocycline; PC, Platelet concentrates; Plt, Platelet; POM, Pomalidomide; TAZ/PIPC, Tazobactam/piperacillin; TEIC, Teicoplanin; VCM, Vancomycin; VGCV, Valganciclovir; VRCZ, Voriconazole.

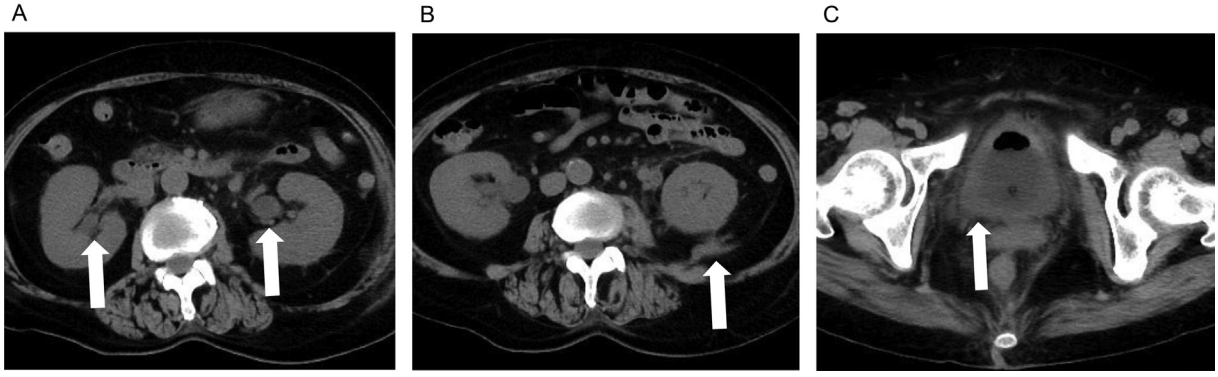

Fig. 2. CT scans on day 21 after commencing POM/DEX. A) The arrow shows dilation of bilateral renal pelvises. She was diagnosed with urethritis. B) The arrow shows the spread of inflammation to the left retroperitoneal space. She was diagnosed with peritonitis. C) The arrow shows bladder wall thickening. She was diagnosed with cystitis.

Table 2
Previous reports of non-HIV adults who developed disseminated ADV infection without receiving allogeneic transplantation.

Case	Age/ Sex	Diagnosis	Treatment***	Period (days) ****	Sites of infections, *Proven/Probable ADV infection	Serum ADV titer (copies/mL)	Antiviral therapy (CDV or RIV)	Response	Outcome
1 [20]	50/M	CLL	Alemtuzumab	NA	Proven, Lung, Spleen, Liver Probable, –	NA	None	PD	Dead**(ADV)
2 [21]	73/M	CLL	Rit CPA	395	Proven, – Probable, Lung, GI tract	3.7×10^5	CDV	CR	Survive
3 [21]	34/F	Breast cancer	ADR CPA	4	Proven, – Probable, Lung, GI tract	3.9×10^7	CDV	PD	Dead**(ADV)
4 [21]	75/F	NHL	Rit CPA	180	Proven, – Probable, Lung, GI tract	9.7×10^9	CDV	PD	Dead**(ADV)
5 [21]	43/M	DLBCL	R-CHOP	6	Proven, – Probable, Lung, GI tract	1.6×10^7	CDV	PD	Dead**(ADV)
6 [22]	46/F	MDS	None	–	Proven, – Probable, Urinary tract, CNS	8.2×10^2	RIV	CR	Survive
7 [23]	20/M	SLE	CHOP	<7	Proven, – Probable, Lung, Urinary tract, CNS, Joint	NA	None	PD	Dead**(ADV)
8 [24]	56/M	CLL	None	–	Proven, BM, Lung, Liver Probable, –	NA	None	PD	Dead**(ADV)
9 (our case)	66/F	MM	aPBSCT, POM/ DEX	36	Proven, – Probable, Urinary tract, Liver, Peritoneum	6.8×10^3	None	PR	Dead**(MM)

Abbreviations: HIV, human immunodeficiency virus; ADV, Adenovirus; CLL, chronic lymphoid leukemia; NHL, non-Hodgkin lymphoma; DLBCL, Diffuse large B cell lymphoma; MDS, myelodysplastic syndrome; SLE, systemic lupus erythematosus; MM, Multiple myeloma; Rit, Rituximab; CHOP, Cyclophosphamide + Adriamycin + Vincristine + Prednisolone; ADR, Adriamycin; CPA, Cyclophosphamide; aPBSCT, autologous peripheral blood stem cell transplantation; POM, Pomalidomide; DEX, Dexamethasone; BM, Bone marrow; RIV, Ribavirin; CDV, Cidofovir; PD, Progressive disease; CR, Complete response; PR, Partial response.
* Proven ADV disease is defined as follows; ADV infection plus corresponding symptoms related to the infection and histological confirmation of ADV in the appropriate location [3].
* Probable ADV disease is defined as follows; ADV infection plus corresponding symptoms and signs without histological confirmation [3].
** Cause of death.
*** The latest treatment for primary disease which is considered to be the direct cause of disseminated ADV infection.
**** Period from starting the latest treatment for primary disease to the onset of disseminated ADV infection.

presence of infection in two or more organs, combined with histopathological documentation of ADV and/or ADV detection (by culture, PCR[25] testing, or antigen detection) from biopsy specimens, bronchoalveolar lavage or cerebrospinal fluid, in the absence of any other offending organisms [1,3,5]. High-level or rising ADV viremia has been reported to predict disseminated ADV disease and death [6–9]. Thus, when ADV disease is suspected in allo-HSCT recipients, surveillance of blood by PCR is the current common practice.

To date, drugs such as RIV, and CDV have been used for ADV infection. RIV is a purine nucleoside analogue with in vitro activity against RNA and DNA viruses. Both successful [10,11] and ineffective [12,13] cases of RIV treatment for ADV infections after allo-HSCT were reported. CDV is an acyclic nucleoside phosphonate analogue used as a broad-spectrum antiviral agent. Its effectiveness was described for the treatment of ADV infections after allo-HSCT [5,14], although its significant side effects (nephrotoxicity, myelosuppression, and uveitis) are major problems. In addition, a recent position statement by the European Society of Blood and Marrow Transplantation recommend the use of CDV as preemptive therapy together with probenecid and hydration in the presence of viremia >1000 copies/mL [15]. For these reasons, antiviral therapy especially for disseminated ADV infection is one of important treatment options based on the prudent evaluation in individual cases. At present, none of these drugs are covered by Japanese insurance. These problems related to the treatment of ADV infections still remain to be solved. A new antiviral drug, brincidofovir, has been reported to have superior anti-ADV activity and a safety profile compared with CDV. Its approval is expected in the near future in Japan [16].

In adult patients, disseminated ADV infection usually occurs in patients receiving allo-HSCT, which requires long-term immunosuppressive therapy. The previously identified risk factors of ADV infection after allo-HSCT include older age, T-cell depletion, HLA matched unrelated or mismatched donor, presence of graft-versus-host disease, use of steroids, and immunosuppressive conditioning regimens [8,17–19]. However, it can rarely occur in patients in other settings as well. Table 2 shows previous reports of patients developing disseminated ADV infection without receiving allo-HSCT [20–24]. Although the underlying diseases predominantly include hematological malignancies, cases with systemic lupus erythematosus and breast cancer were reported. Four patients developed disseminated ADV infection soon after chemotherapy or antibody therapy, while two patients developed it after long-term immunosuppressive therapy. Notably, the other two patients developed disseminated ADV infection without immunosuppressive treatment. The major sites of ADV infection were bone marrow, lung, liver, urinary tract, central nervous system, gastrointestinal tract, and spleen. Antiviral therapy with RIV or CDV was effective in two of five cases. Six of nine cases died of ADV infection, indicating its high mortality rate even in patients not receiving allo-HSCT.

Our patient had severe immunodeficiency due to progression of MM and repeated chemotherapy followed by auto-PBSCT within a short time period. Although the immune-reconstitution after auto-PBSCT occurs more rapidly than that after allo-HSCT [25], it might be suboptimal in the patients with poor primary disease control [26]. These factors may cause the development of disseminated ADV infection in our case. Although the precise frequency of opportunistic viral infections caused by IMiDs is unveiled, increased risk of serious infections caused by IMiDs has recently been reported [27]. In fact, there is a report of disseminated herpes simplex virus and varicella zoster virus infection in a patient with MM receiving thalidomide, which possibly caused immunosuppression and opportunistic viral infections [28]. This suggests that we need to be vigilant for opportunistic infections in patients who receive repeated salvage therapies using IMiDs, as with our case.

We believe that one reason for our patient's favorable outcome after fatal disseminated ADV infection was her relatively low serum ADV titers. As with patient numbers 3–5 in Table 2, high serum ADV titers are likely associated with ADV dissemination and death in non-allogeneic transplant settings [6–9]. Thus, early diagnosis and interventions are important for improving the prognosis. However, disseminated ADV infection is not common and sometimes difficult to diagnose at hospitals that do not perform allo-HSCT. Additionally, the PCR-based virus detection is available in limited hospitals. These are the problems to be solved in the future.

[25] PCR, polymerase chain reaction.

In summary, disseminated ADV infection can occur in severely immunocompromised hosts even in non-allogeneic transplant settings. We need to be vigilant for opportunistic viral infections in patients with MM who receive auto-PBSCT and repeated salvage therapies. Although disseminated ADV infection is a rare event, its mortality rate is very high, and hence, early diagnosis and interventions are required in suspected cases.

Conflicts of interest

The authors have no conflicts of interest.

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