INTERNAL MEDICINE

□ CASE REPORT □

Rapid Multiorgan Failure due to Large B-cell Lymphoma Arising in Human Herpesvirus-8-associated Multicentric Castleman's Disease in a Patient with Human Immunodeficiency Virus Infection

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Abstract

A 46-year-old man presented with a high-grade fever, multiple lymphadenopathies, hepatosplenomegaly and human immunodeficiency virus (HIV) seropositivity, without severe immunosuppression. We suspected human herpesvirus-8 (HHV-8)-associated multicentric Castleman's disease (MCD) based on the results of a physical examination and laboratory investigations, including bone marrow aspiration. However, the patient died eight days after admission due to multiorgan failure. An autopsy revealed MCD and lymphoma cell infiltration in multiple organs. The final diagnosis was large B-cell lymphoma (LBCL) arising in HHV-8-associated MCD. This case illustrates the potential for LBCL in HHV-8 MCD in HIV-infected patients with hepatosplenomegaly and lymphadenopathy without severe immunosuppression and highlights the clinical significance of bone marrow aspiration.

Key words: MCD, LBCL, HHV-8 MCD, HIV, bone marrow aspiration

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Introduction

Castleman's disease is a benign lymphoproliferative disease, first described by Castleman et al. in 1956 (1). Human herpesvirus-8 (HHV-8)-associated multicentric Castleman's disease (MCD) is fatal; such patients display HHV-8 infected lymphoid cells with an IgM-expressing plasmablast-like appearance and an increase in the number of plasma cells in the lymph nodes. In addition, MCD frequently progresses to lymphoma, most commonly large B-cell lymphoma (LBCL) (2). The occurrence of LBCL in the setting of HHV-8 MCD involves the monoclonal proliferation of HHV-8-infected lymphoid cells (3) and usually occurs in patients co-infected with HHV-8 and human immunodeficiency virus (HIV). Unlike other HIV- and HHV-8-related malignant diseases, such as primary effusion lymphomas and Kaposi's sarcoma (KS), LBCL in HHV-8 MCD can arise in patients without severe immunosuppression. Furthermore, the incidence of KS in HIV patients has decreased due to the introduction of anti-retroviral therapy (ART), although ART cannot be used to combat MCD (4). Therefore, although though MCD is rare, and the development of LBCL in HHV-8 MCD even more rare, making an early diagnosis of MCD is important. We herein report a case of multiorgan failure that rapidly progressed due to the onset of LBCL in an HIV patient with HHV-8 MCD.

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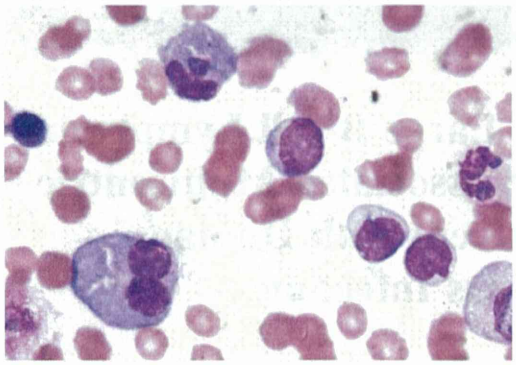

Figure 1. **Bone marrow aspiration smear (×1,000) revealing plasma-shaped cells with abnormal nuclei, but no large blast cells.**

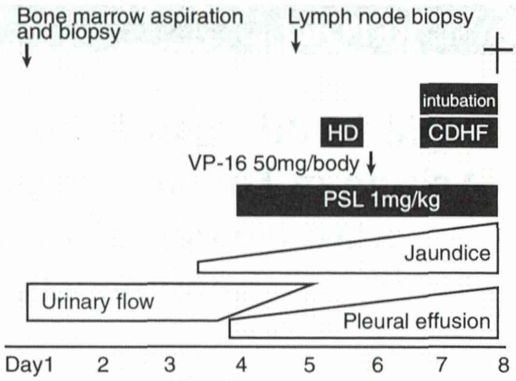

Figure 2. **Clinical course of this case study. The urinary flow gradually decreased, which was followed by the development of jaundice, pleural effusion, severe acute renal failure, coma, and hypotension. Despite intensive intervention, the patient died 8 days after admission. CHDF: continuous hemodialysis filtration, HD: hemodialysis, PSL: prednisolone, VP-16: etoposide**

Case Report

A 46-year-old man was transferred to our hospital due to a high fever, fatigue, diarrhea, anemia, thrombocytopenia and HIV seropositivity. The high fever and fatigue had persisted for six months prior to admission, while the diarrhea and severe fatigue developed a few days before admission. A physical examination revealed an increased respiratory rate and anemia without hemorrhage. The results of a peripheral blood test indicated HIV seropositivity, severe anemia, thrombocytopenia, hypoalbuminemia and an elevated level of C-reactive protein (CRP). With respect to the HIV status, the HIV-RNA copy number in the plasma was elevated at 2.2×10^6 copies/mL, whereas the CD4-positive T lymphocyte count (CD4) was suppressed at 254/μL. A computed tomography (CT) scan revealed hepatosplenomegaly and multiple lymphadenopathies throughout the patient's body. Based on these findings, we suspected MCD. Therefore, additional blood examinations were performed, the results of which demonstrated elevated levels of interleukin (IL)-6 and soluble IL-2 (sIL-2) receptors in the serum. In addition, HHV-8 DNA was detected in the peripheral blood, at 4.2×10^5 copies/million cells [real-time polymerase chain reaction (PCR)]. Furthermore, the IgG and IgM levels were slightly elevated, and the M bow was not observed on immunoelectrophoresis, which suggested a pattern of chronic inflammation. An analysis of the bone marrow aspirate revealed 16% of the cells to be plasma cells with abnormal nuclei (Fig. 1). However, no signs of hemophagocytic syndrome were found in the specimen. The patient's clinical course is summarized in Fig. 2. On day 4 of hospitalization, steroid therapy with prednisolone [1 mg/(kg/day)] was started as antitumor treatment and to suppress the severe inflammation (5). Nevertheless, after the introduction of prednisolone, acute renal failure developed, requiring hemodialysis, although there was no evidence of acute tumor lysis syndrome. The following day, VP-16 therapy was introduced as chemotherapy for MCD (5), as we were unable to wait for a definitive diagnosis. The patient's condition continued to worsen, and he subsequently required respiratory management and continuous hemodialysis filtration due to severe acute renal failure, coma and low blood pressure. Despite these intensive interventions, he died eight days after admission. An analysis of the lymph node specimen of the neck (a lymph node biopsy of the patient's neck was performed on day 4 of hospitalization) revealed the presence of numerous plasma cells and small lymphoid cells with an onionskin appearance, both of which are characteristic of Castleman's disease. In addition, hyalinized blood vessels were prominent (Fig. 3). An analysis of another portion of the specimen revealed lymphoid cells with large abnormal nuclei gathered locally that were found to be $CD3^-$, $CD20^+$, $CD38^+$, $CD138^-$, $CD79a^{-/+}$ and $Ki\text{-}67^+$ as well as positive for KS-associated herpesvirus-related latent nuclear antigen-1 (LANA-1) and negative for Epstein Barr virus (EBV)-encoded RNA-1 (EBER) (Fig. 4). An autopsy revealed invading tumor cells at other sites in the lymph nodes and multiple organs, including the spleen, liver, kidneys and lungs. It was difficult to differentiate between MCD and LBCL in HHV-8 MCD.

Discussion

MCD is a very rare disease, with cases in which the condition is comorbid with LBCL being even more rare. In the present case, the diagnosis of MCD was made based on the findings of a clinical examination, laboratory tests and an analysis of the bone marrow aspirate. In 2007, Gerard et al. defined the diagnostic criteria for MCD (6). These criteria were met in the current case, as the patient had a high-grade fever, cough, nasal obstruction, elevated serum CRP level, multiple lymphadenopathies, splenomegaly, pleural effusion and jaundice, despite the absence of autoimmune anemia. However, little is known about the findings and clinical importance of bone marrow aspiration in cases of MCD (7). In

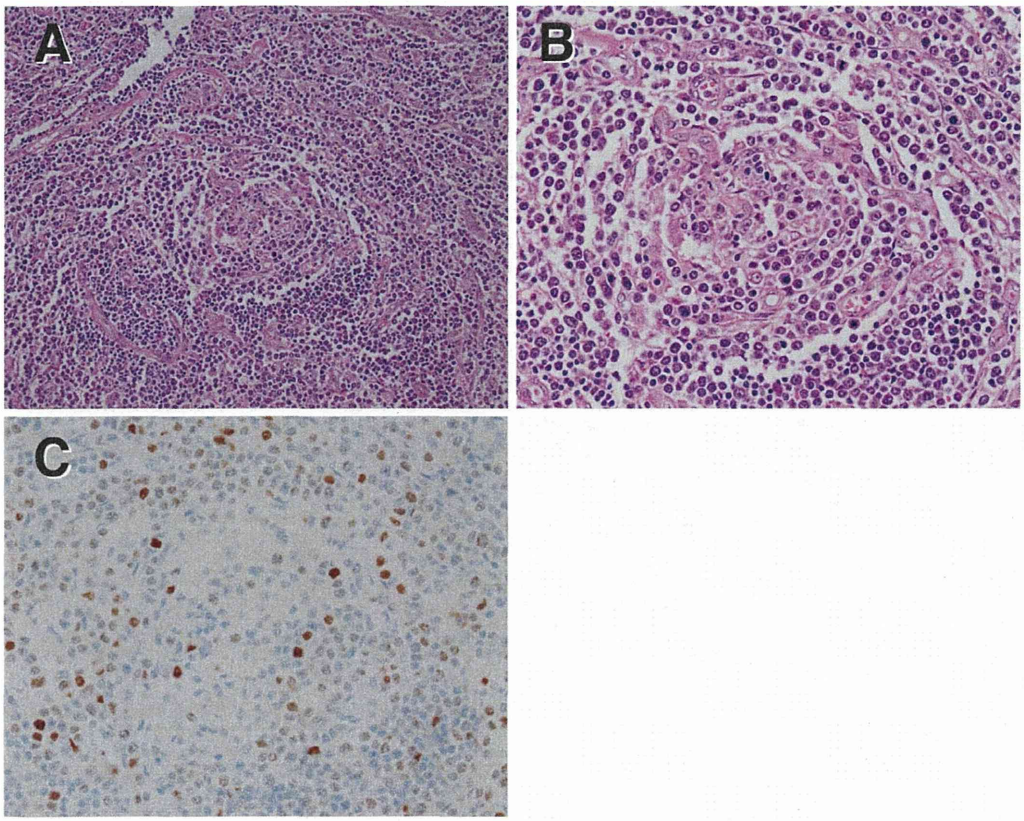

Figure 3. **Biopsy specimen of the patient's right neck lymph node performed on day 4. A: Hematoxylin and Eosin (H&E) staining (×200). Plasma cells and small lymphoid cells arranged concentrically (onionskin appearance). B: H&E staining (×400). Numerous invading plasma cells, small lymphoid cells, and pronounced hyalinized blood vessels can be seen. C: LANA-1 staining (×400). Plasma cells stain positive in a circular fashion**

a recent study, Venkataraman et al. reported the predominance of plasmacytosis in bone marrow biopsy specimens in patients with MCD (8, 9). In the current case, we reconfirmed that bone marrow aspiration is an effective diagnostic approach, despite the absence of plasmablasts or atypical lymphocytes among peripheral blood cells, as the findings were similar to those associated with multiple myeloma. Moreover, no signs of bone marrow infiltration of lymphomas were found, and λ-chain restriction was present on flow cytometry in the lymph node biopsy specimen only, not in the peripheral blood. Based on these findings, we recommend performing bone marrow aspiration in cases in which MCD is suspected.

The potential for LBCL with HHV-8-associated MCD should be considered in HIV-infected patients with anemia, splenomegaly and a high fever who exhibit an elevated serum level of CRP without any evidence of bacterial infection (10). HHV-8 infection is common among men who have sex with men in Japan and can cause primary effusion lymphoma, KS and LBCL in HHV-8 MCD (11). Furthermore, the burden of HHV-8 infection, quantified using a PCR-based assay, together with the serum CRP and IL-6 levels, correlates with the MCD activity (2, 5, 12).

Unlike KS, the most common disease caused by HHV-8 infection in HIV-infected patients, the extent of MCD and LBCL in HHV-8 MCD cases is only weakly correlated with the CD4 count or administration of ART. Moreover, relapse is frequent. In the present case, however, the CD4 count in the peripheral blood was greater than 200/μL, and the patient was not severely immunocompromised. Therefore, regardless of the CD4 and ART status, the possibility of LBCL in HHV-8 MCD should be considered when an HIV-infected patient presents with clinical and laboratory findings similar to those described here. It is also noteworthy that our patient had elevated levels of CRP, IL-6 and sIL-2 receptor, suggesting that he experienced a cytokine storm due to the malignant lymphoma (Table). Hence, lymph node biopsies are also required in such cases.

LBCL in HHV-8 MCD is associated with the monoclonal proliferation of HHV-8-infected lymphoid cells, which express both IgM and viral IL-6 and exhibit a stippled nuclear staining pattern for LANA-1. The WHO classification describes these cells as being $CD20^{-/+}$, $CD79a^{-}$, $CD138^{-}$, $CD38^{-/+}$ and $EBER^{-}$, although an alternative classification has been proposed in which the presence of EBV, HIV and HHV-8 is considered to be a marker of this cell type (8). The immunophenotype observed in this case was slightly different from that specified in the WHO classification but

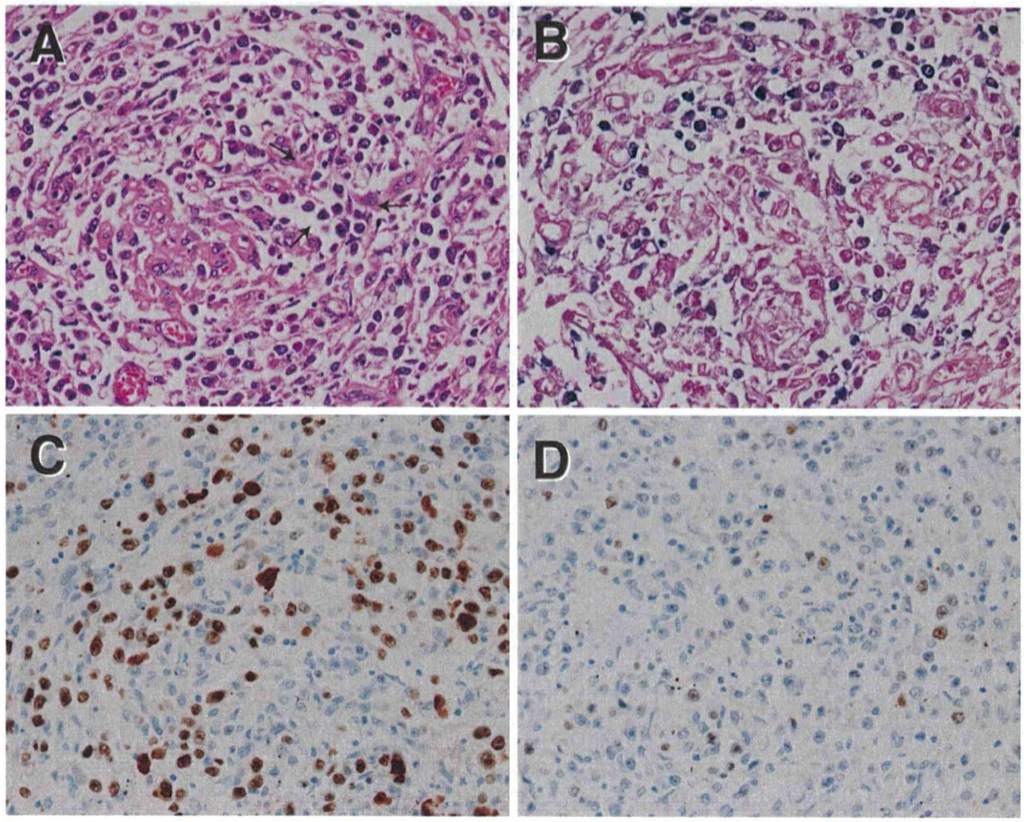

Figure 4. **Analysis of another part of the specimen of the biopsy revealed localized accumulation and scattered infiltration of lymphoid cells with large abnormal nuclei (arrows), which were positive for lambda protein (in situ hybridization), Ki-67, and LANA-1. A: Hematoxylin and Eosin staining (×400). B: lambda protein staining (×400). C: Ki-67 staining (×400). D: LANA-1 staining (×400)**

Table. **Laboratory Test Results on Admission**

Biochemistry		Hematology		Coagulation	
TP	6.8 g/dL	WBC	8,800/μL	aPTT	62.6 s
Alb	1.7 g/dL	Neut	43%	PT	21.6 s
AST	37 IU/L	Lym	51%	FDP	20 μg/mL
ALT	9 IU/L	Mono	4.90%	D-dimer	5.19 μg/mL
ALP	461 IU/L	CD4TLym	254/μL	Fib	644 mg/dL
LDH	393 IU/L	RBC	1.95×10^6/μL	PIC	1.4 μg/mL
T-Bil	0.6 mg/dL	Hb	5.7 g/dL	TAT	2.7 μg/L
BUN	19 mg/dL	Ht	17.80%	Haptoglobin	60 mg/dL
Cre	1.01 mg/dL	Plt	3.0×10^4/μL		
Na	131 mEq/L				
K	4.5 mEq/L	Infection			
Cl	97 mEq/L	HIV-RNA	2.2×10^6 c/mL		
CRP	30.8 mg/dL	HHV-8 DNA	4.2×10^5 c/mL		
sIL-2R	12,100 mg/dL				
IL-6	262 pg/mL				
IgG	2,609 mg/dL				
IgA	199 mg/dL				
IgM	339 mg/dL				

sufficiently similar to be considered LBCL in HHV-8 MCD.

Currently, the number of HIV-infected patients in Japan is increasing; therefore, the incidence of cases similar to the one described in this report may also increase. We hope that additional case studies will help to further refine the diagnosis and treatment of this rare but fatal disease.

The authors state that they have no Conflict of Interest (COI).

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Case report

A case of non-cirrhotic portal hypertension associated with anti-retroviral therapy in a Japanese patient with human immunodeficiency virus infection

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ABSTRACT

The diagnosis of non-cirrhotic portal hypertension (NCPH), a rare but potentially life-threatening complication in human immunodeficiency virus (HIV)-positive individuals, often occurs only after the emergence of fatal manifestations such as bleeding of esophageal varices. We herein report a female Japanese HIV patient who developed NCPH approximately 4 years after discontinuation of 65 months of didanosine (ddI) administration. The patient presented with severe ascites, bloody bowel discharge, extreme abdominal swelling, and symptoms of portal hypertension but no sign of liver cirrhosis. Examination revealed esophageal varices, oozing-like bleeding from a wide part of the colon, significant atrophy of the right lobe of the liver, and arterio-portal shunting and recanalization from the left medial segment branch of the portal vein to a paraumbilical vein, but no visible obstruction of the main trunk of the portal vein. Treatment for esophageal varices consisted of coagulation therapy with argon plasma after enforcement by endoscopic sclerotherapy and oral administration of β-blockers for elevated portal blood pressure. The patient has not experienced gastrointestinal bleeding in the approximately 5 years since the diagnosis of NCPH. Reviewing this case suggests the importance of suspecting NCPH in HIV patients with liver dysfunction of unknown etiology with a history of ddI and other purine analogs use, as well as the importance of controlling portal hypertension and esophageal varices in the treatment of NCPH.

1. Introduction

Non-cirrhotic portal hypertension (NCPH) is a rare but potentially life-threatening complication experienced by human immunodeficiency virus (HIV)-positive individuals [1]. This condition has become increasingly recognized as a cause of liver morbidity and mortality among HIV patients whose status is otherwise well-controlled. The most important predisposing factor to its development has been identified as exposure to didanosine (ddI). Although over 70 cases of NCPH in HIV patients throughout the world have been reported to date, few of these reports have concerned Asian patients [2]. Here we report the development of NCPH in a female Japanese HIV patient approximately 4 years after discontinuation of 65 months of ddI administration. To our knowledge, our patient represents the first case of NCPH diagnosed with liver biopsy in an HIV-positive individual in Japan.

2. Case report

A 35-year-old Japanese woman was admitted to our hospital with a large quantity of ascitic fluid and bloody bowel discharge. Although she was diagnosed of HIV infection in 1993 with CD4 count of 109 cells/mm^3, she did not present with AIDS. She did not have a history of excessive alcohol consumption.

After initiation of anti-retroviral therapy with azidothymidine (AZT) and lamivudine (3 TC) in 1999, the patient was referred to our hospital in 2000 and her anti-retroviral regimen was changed to stavudine (d4T), ddI, and nevirapine (NVP) therapy in preparation

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Table 1
Laboratory data at the onset of non-cirrhotic portal hypertension.

Blood cell count parameters			Blood chemistry parameters		
WBC	6700	Cells/μL	AST	83	IU/L
RBC	1.35	$\times 10^4$ cells/μL	ALT	82	IU/L
Hb	4.2	g/dL	LDH	271	IU/L
Hct	16.2	%	T-Bil	0.2	mg/dL
Plt	20.7	$\times 10^4$ cells/μL	ALP	268	U/L
Coagulation parameters			γ-GTP	54	U/L
APTT	33.6	sec	NH3	43	μg/dL
PT	15.9	sec	CPK	59	IU/L
PT-INR	1.26		Cre	0.5	mg/dL
PT	72.0	%	BUN	9	mg/dL
Fibrinogen	148	mg/dL	Na	139	mEq/dL
HIV parameters			K	4.1	mEq/dL
CD4 count	110	cells/mm^3	Cl	104	mEq/dL
HIV-RNA	<40	copies/mL	CRP	0.08	mg/dL

WBC: white blood cell; RBC: red blood cell; Hb: hemoglobin; Hct:hematocrit; Plt: platelet; APTT: activated partial thromboplastin time; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; T-Bil: total bilirubin; ALP: alkaline phosphatase; γ-GTP: γ-glutamyl transpeptidase; CPK: creatine phosphokinase; Cre: creatinine; BUN: blood urea nitrogen; Na: sodium; K: potassium; Cl: chloride; CRP: C-reactive protein.

for delivery. It had subsequently been changed to AZT, ddI, and NVP in 2004 and to tenofovir (TDF), 3 TC, and NVP in 2005. During this period, her level of HIV-RNA was below the detectable level (<50 copies/mL), and her CD4 count had been stable at around 100 cells/mm^3.

Since 2007, the patient's hemoglobin level had gradually decreased from 10 to 7 g/dL. We suspected that a gynecologic disorder was responsible for this decrease, and performed intravaginal ultrasonography. Although the result revealed a small amount of ascites of the floor of the pelvis, subsequent endocervical cytologic testing showed no signs of malignancy. The patient experienced temporary improvement upon administration of an oral and intravenous iron preparation, which was subsequently administered several times after gynecological inspection. While her serum vitamin B12 and folic acid levels were within normal ranges, her liver enzyme levels were slightly elevated. Despite the scheduling of more invasive means of examination, including gastrointestinal endoscopy, the patient refused to undergo them.

Three months after her visit to the gynecology department, the patient was admitted to the emergency room with massive ascites, bloody bowel discharge, and extreme abdominal fullness. Her body weight was 12 kg higher than her usual weight, her blood pressure was 104/72 mmHg, and her pulse rate was 128 beats per minute. Laboratory testing indicated that she had severe anemia with hemoglobin and hematocrit levels of 4.2 g/dL and 16.2%, respectively (Table 1). Although her liver enzyme levels were mildly elevated, coagulation tests yielded no abnormal findings (Table 2).

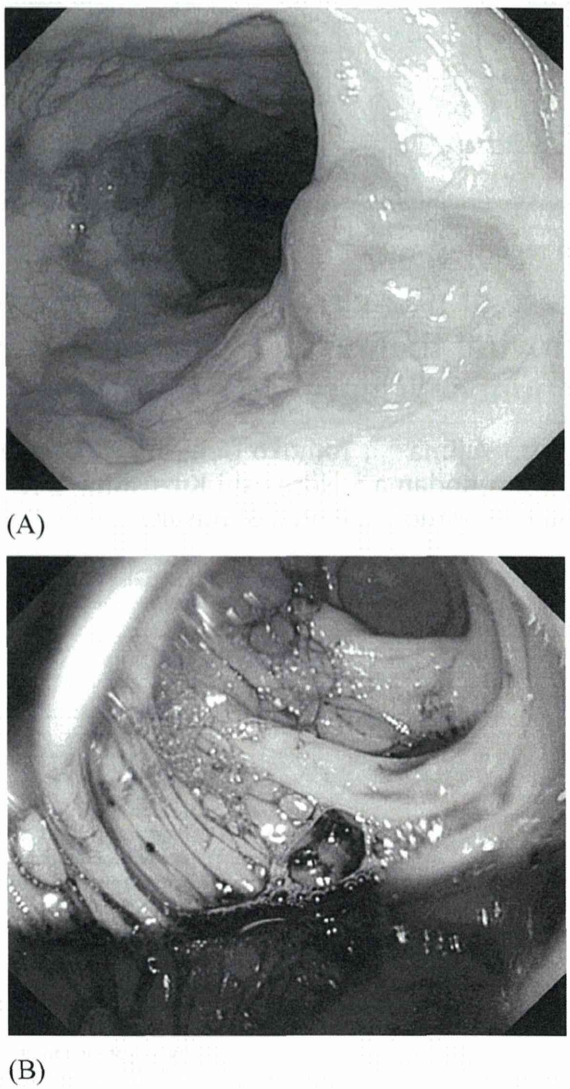

Fig. 1. (A) Urgent upper gastrointestinal tract endoscopy showing esophageal varices (Ls, F3, Cb, and RC-). (B) Massive oozing-like bleeding from a wide part of the colon.

Urgent upper-gastrointestinal tract endoscopy showed esophageal varices (Ls, F3, Cb, and RC-; Fig. 1A) and colonoscopy revealed oozing-like bleeding from a wide part of the colon (Fig. 1B). Abdominal ultrasonography and computed tomography (CT) scan (Fig. 2) revealed a large quantity of ascites, significant atrophy of the right lobe of the liver, and significant splenomegaly (spleen index 107.97 cm^2). A three-dimensional vascular image restructured

Table 2
Summary of liver function, ascites, endoscopic, and immunological findings.

Date (y/m)		AST (IU/L)	ALT (IU/L)	ALP (U/L)	Ascites	Endoscopic findings	CD4 count (Cells/mm^3)	HIV-RNA (Copies/mL)	ART regimen
2000/07	First visit	19	13	221	NP	NP	222	3800	d4T + ddI + NVP
2009/07	3 months before onset	50	70	226	Small	NP	140	<40	TDF+3 TC + NVP
2009/10	Onset of NCPH	83	82	268	Massive	Ls, F3, Cb, RC-	110	<40	TDF+3 TC + NVP
2010/10	One year after onset	59	65	277	Small	Ls, F2, Cb, RC-	110	<40	RAL + ETR
2014/04	4.5 years after onset	25	20	228	Small	Li, F1, Cb, RC-	177	<20	RAL + ETR

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ART: antiretroviral therapy; NP: not performed; Ls: locus superior; Li: locus inferior; F3: largest size varices; F2: enlarged tortuous varices; F1: small and straight varices; Cb: blue varices; RC: red color sign; d4T: stavudine; ddI: didanosine; NVP: nevirapine; TDF: tenofovir; 3 TC: lamivudine; RAL: raltegravir; ETR: etravirine.

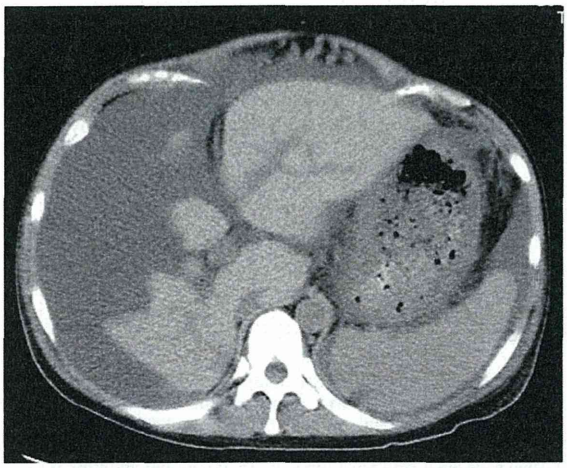

Fig. 2. Computed tomography scan showing a large quantity of ascites and significant atrophy of the right lobe of the liver.

using CT indicated arterioportal shunting and recanalization from the left medial segment branch of the portal vein (P4) to a paraumbilical vein, but no visible obstruction of the main trunk of the portal vein.

Serological antibody examinations for hepatitis A, B, C, D, and E were negative, and DNA level of hepatitis virus B and RNA levels of hepatitis virus C and E were under detectable limits. As no abnormal findings were obtained for anticardiolipin-β-2 glycoprotein I complex antibody, a mitochondrial M2 antibody, and lupus anti core grant antinuclear antibody, a rheumatoid factor antibody, autoimmune disease was ruled out. Regarding coagulation markers, the free-form protein S antigen level was slightly decreased, but prothrombin time, protein C level, and antithrombin III level were within normal ranges.

Liver biopsy revealed no fibrosis but mild ferrugination, narrowing of the peripheral portal vein, and a decrease of the portal region in number (Fig. 3A and B). Fibroscan revealed no evidence of cirrhosis (stiffness: 9.3 kPa, IQ: 1.1 kPa, CS: 9.2 kPa). On the basis of these findings, NCPH due to ddI was diagnosed and the antiretroviral regimen was changed from TDF, 3 TC, and NVP to raltegravir and etravirine to avoid use of NRTIs.

Single coagulation therapy with argon plasma was performed after 3 sessions of endoscopic sclerotherapy for treatment of esophageal varices over 2 years. Oral administration of β-blockers and diuretic (spironolactone) were initiated to decrease the portal blood pressure and control ascites, respectively. After 2 years of endoscopic procedures, subsequent annual endoscopy showed no signs of recurrence of esophageal varices that required an additional endoscopic treatment. Abdominal ultrasonography performed every 6 months, revealed a small amount of ascites and splenomegaly. A recent CT scan showed no apparent change in collateral circulation of the portal flow and recent laboratory testing revealed an increase in hemoglobin count to 10–11 g/dL and liver enzyme levels within normal range.

Approximately 60 months from the onset of massive ascites, the patient, from whom informed consent regarding publication of a report on her case and the use of photographs was obtained, has experienced no apparent gastrointestinal bleeding or shown any signs of hepatocellular carcinoma.

3. Discussion

Although a relatively rare disease, NCPH is gradually becoming recognized as a clinical condition in HIV-positive individuals

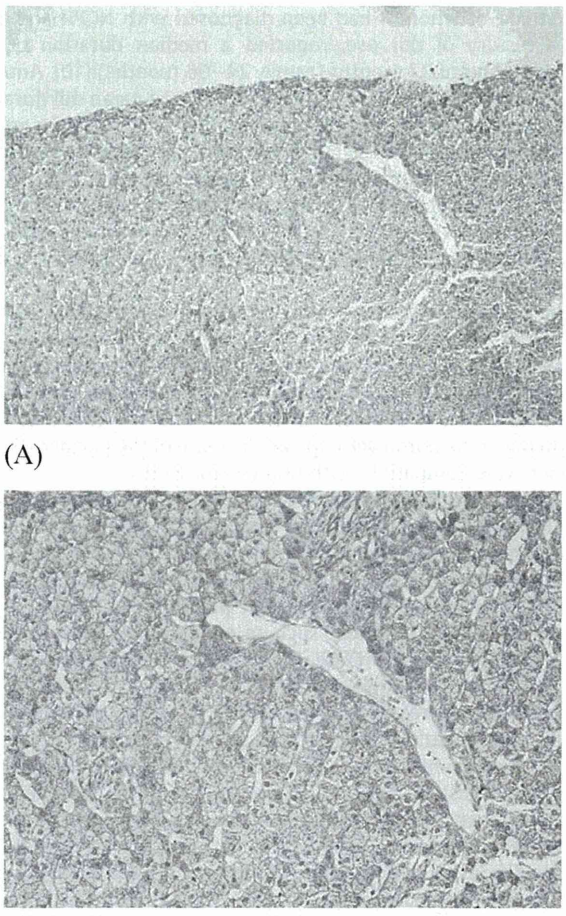

Fig. 3. A: hematoxylin and eosin,×100, B: hematoxylin and eosin,×400 Liver biopsy showing no sign of liver fibrosis but narrowing of the peripheral portal vein and decrease of the portal region.

receiving antiretrovirals. Since the first case described in HIV-positive individuals by Maida et al. [1], over 70 cases have been reported. Exposure to hepatotoxic materials, such as arsenic, chloroethylene, copper sulfate, and azathioprine (a purine analog), thioguanine (6-thioguanine), and mercaptopurine (6-mercaptopurine) are recognized as causes of this condition [3–5]. As almost all reports have suggested that ddI contributes to NCPH development as a causative agent [6,7], in 2010, the US Food and Drug Administration suggested the existence of an association between ddI and NCPH [8].

Most cases of NCPH present with liver function abnormality before diagnosis. In our case, mild elevation of transaminase level, which was suspected to be an adverse event of NVP, persisted for several years before NCPH onset. A likely cause of this increase in transaminase level was NCPH development. Neil et al. proposed that thrombocytopenia, splenomegaly, didanosine use, elevated aminotransferase level, and elevated alkaline phosphatase level are highly prevalent in NCPH patients, all of which were observed in our case with the exception of thrombocytopenia [9].

In the present case, ddI had been administered for approximately 65 months prior to its discontinuation, which was approximately 4 years before the onset of NCPH. A large 20-year trial that retrospectively examined approximately 8460 HIV-positive

individuals, of whom 8 had been diagnosed with NCPH and all 8 had a history of ddI use, reported a median duration of ddI administration of 37 months (range, 24–66 months) [10]. Another review of literature of 61 NCPH cases reported a mean ddI duration of 65 months (range, 13–111 months) [2]. The durations of ddI administration reported by these literature are consistent with our case. Short-term administration of a combination of d4T and ddI, which Schouten et al. reported as a risk factor for NCPH, might have been a factor in the onset of NCPH in our patient as well [11].

A pathological diagnosis by liver biopsy is essential for a diagnosis of NCPH.

The 2 characteristic pathologic findings for diagnosis are the (1) absence of bridging cirrhosis, and (2) presence of nodular regenerative hyperplasia [12], the latter of which indicates immune dysfunction, auto-immune disease, and portal hypertension. In our patient, the lack of evidence of cirrhosis and the observation of narrowing of the portal vein tip and decrease of the portal region in number were compatible with findings for NCPH.

In this case, ddI use had been discontinued long before the onset of NCPH. β-blockers and diuretic were started, and endoscopic injection sclerotherapy and endoscopic variceal ligation were chosen for consolidation therapy for treatment of varices. The international guidelines for treatment of idiopathic portal hypertension recommend endoscopic treatment such as endoscopic variceal ligation from the perspectives of efficacy and safety as secondary preventive treatment after a bleeding episode. More invasive therapies such as balloon-occluded retrograde transvenous obliteration and transjugular intrahepatic portosystemic shunting can be selected as optional treatments under special conditions [13]. Although liver transplant is also an option, it poses the risk of NCPH recurrence after the transplant from the perspective of pathogenesis. Thus, no invasive therapies were planned for our patient, whose NCPH status is well controlled at the time of this reporting. Although a good survival rate has been reported for HIV-negative NCPH patients, the long-term prognosis of HIV-positive NCPH remains unclear. Prompt diagnosis, discontinuation of contraindicating agents (such as ddI), and appropriate management of portal hypertension are required to control HIV-associated NCPH.

Diagnosis of NCPH, a rare but potentially life-threatening complication in HIV-positive individuals, is often delayed until the emergence of fatal manifestations such as bleeding of esophageal varices. Thus, HIV experts must be aware and be knowledgeable about this clinical condition. NCPH can develop in an HIV patient years after cessation of ddI administration as this case showed. NCPH should be suspected when patients with a history of ddI and other purine analogs, such as abacavir and azathioprine, present with liver dysfunction of unknown etiology and/or anemia.

Conflict of interest

None.

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The prevalence of opportunistic infections and malignancies in autopsied patients with human immunodeficiency virus infection in Japan

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Abstract

Background: Opportunistic infections and malignancies such as malignant lymphoma and Kaposi sarcoma are significant complications of human immunodeficiency virus (HIV) infection. However, following the introduction of antiretroviral therapy in Japan in 1997, the incidence of clinical complications has decreased. In the present study, autopsy cases of HIV infection in Japan were retrospectively investigated to reveal the prevalence of opportunistic infections and malignancies.

Methods: A total of 225 autopsy cases of HIV infection identified at 4 Japanese hospitals from 1985–2012 were retrospectively reviewed. Clinical data were collected from patient medical records.

Results: Mean CD4 counts of patients were 77.0 cells/μL in patients who received any antiretroviral therapy during their lives (ART (+) patients) and 39.6 cells/μL in naïve patients (ART (−) patients). Cytomegalovirus infection (142 cases, 63.1%) and *pneumocystis* pneumonia (66 cases, 29.3%) were the most frequent opportunistic infections, and their prevalence was significantly lower in ART (+) patients than ART (−) patients. Non-Hodgkin lymphoma and Kaposi sarcoma were observed in 30.1% and 16.2% of ART (−) patients, and 37.9% and 15.2% of ART (+) patients, respectively. Malignant lymphoma was the most frequent cause of death, followed by cytomegalovirus infection regardless of ART. Non-acquired immunodeficiency syndrome (AIDS)-defining cancers such as liver and lung cancer caused death more frequently in ART (+) patients (9.1%) than in ART (−) patients (1.5%; $P = 0.026$).

Conclusions: The prevalence of infectious diseases and malignancies were revealed in autopsy cases of HIV infection in Japan. The prevalence of cytomegalovirus infection and *pneumocystis* pneumonia at autopsy were lower in ART (+) patients than ART (−) patients. Higher prevalence of non-AIDS defining malignancies among ART (+) patients than ART (−) patients suggests that onsets of various opportunistic infections and malignancies should be carefully monitored regardless of whether the patient is receiving ART.

Keywords: AIDS, Opportunistic infections, Autopsy, Antiretroviral therapy

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