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Case Report

Acute kidney injury and inflammatory immune reconstitution syndrome in mixed genotype (A/E) hepatitis B virus co-infection in HIV-associated lymphoma

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Abstract: We report a first case of HIV-associated lymphoma (HAL) presenting with acute kidney injury (AKI) and inflammatory immune reconstitution syndrome (IRIS). A 39-year-old male, treated with nonsteroidal anti-inflammatory drugs (NSAIDs) for one month prior to admission, developed AKI, left testicular tumor, and recurrent swelling of the right parotid gland. A resected testicular tumor exhibited features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. Renal biopsy showed hydro-degeneration of renal tubules, interstitial inflammatory cells, and a small number of lymphoma cells in the sub-capsule, compatible with acute interstitial nephritis. His renal dysfunction rapidly recovered following chemotherapy and combination antiretroviral therapy (cART). He developed pneumonia concomitantly with a decrease in HIV-RNA level and an increase in CD4+ cells after the first cycle of chemotherapy, which spontaneously resolved after the second cycle of chemotherapy without additional anti-infection drugs; thus, his pneumonia fulfilled the diagnostic criteria for IRIS. We suggest that IRIS may frequently develop during chemotherapy for HAL, but may be overlooked. He was coinfected with hepatitis B virus (HBV), which genotypes known as is associated with liver-related mortality and response to antiviral therapy; recently, an intimate interplay between HIV and HBV in the onset of lymphoma has been reported. Therefore, we addressed the HBV genotype in the patient. The analysis revealed that he exhibited a mixed genotype (A/E) not native to Japan and primarily found in Europe and North America or West Africa. These findings suggest that universal vaccination for juveniles against HBV is warranted in Japan.

Keywords: Hepatitis B virus, HIV, genotype, immune reconstitution inflammatory syndrome, acute kidney injury, ptosis

Introduction

The survival of patients with HIV-associated lymphoma (HAL) has improved substantially and currently, due to the widespread use of combination antiretroviral therapy (cART), it appears to be comparable to HIV-negative lymphoma patients. Epidemiologically, HIV-seropositivity increases the risk of developing lymphoma by 60–200-fold [1, 2]. A recent cohort study demonstrated that hepatitis B virus (HBV) infection increased the risk of lymphoma (adjusted hazard ratio 1.74) [3]. Patients with HIV infection are likely to exhibit higher HBV DNA levels for a longer duration, and increase liver-related morbidity [4, 5]. Thus, there may be a close correlation between HIV and HBV in the pathogenesis of lymphoma. Several studies have suggested that the HBV genotype, classified into eight genotypes (A to H) with characteristic geographical distribution worldwide, may correlate with the development and age-related incidence of hepatocellular carcinoma (HCC) or activity of hepatitis, or may affect patient response to antiviral treatment [6-8]. Although approximately 10% of HIV-

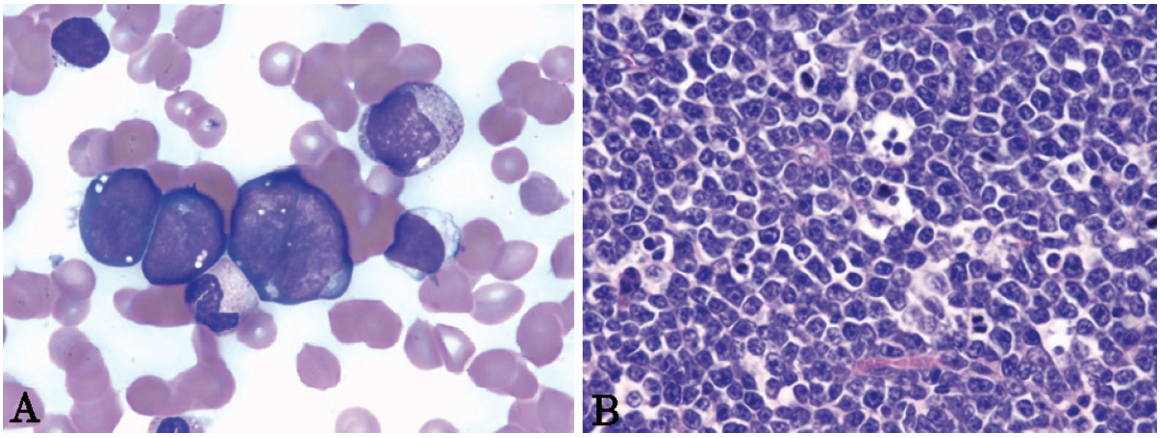

Figure 1. A. Bone marrow aspiration (May-Giemsa stain). Large convoluted cells are shown. B. Testicular tumor shows features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma.

positive patients are carriers of HBV, there are few reports on the prevalence of HBV infection in HAL [9, 10]. Furthermore, the relevance of HBV genotypes in HAL has never been addressed, and the characteristics of these co-infected patients remain unknown. Therefore, in this study we addressed HBV genotype and identified the first case of mixed genotype (A/E) HBV infection in HAL.

Several pathogenetic factors may drive acute kidney injury (AKI) in HIV-infected patients [11-15]. In HAL patients, additional factors, including anticancer drugs or lymphoma itself, may be involved in the onset of AKI. Thus, it is even more challenging to identify the pathogenetic factors of AKI in HAL. Inflammatory immune reconstitution syndrome (IRIS) is common in HIV infected patients; however, there have been only two previous reports in HAL [16]. In this study, we discuss AKI and IRIS pathogenesis and treatment for this patient.

Case report

A 39-year-old Japanese male was referred to our hospital due to systemic edema. He had experienced several sexual contacts with females approximately 15 years ago. Two months ago, he was involved in a traffic accident, and thereafter continued to experience numbness in the left submandibular region and recurrent swelling of the right parotid gland. Computed tomography (CT) revealed a fracture at submandibular bone and a mass lesion 25 mm in diameter in the right parotid gland. He had been previously treated with non-steroidal anti-inflammatory drugs (NSAIDs) for one month at a clinic, but his symptoms did not improve. On admission to the hospital, he presented with fever (38.2°C), massive ascites, left testicular mass, systemic lymph node swelling, and systemic edema. CT with no enhancement revealed bilateral swelling of the kidneys with low or heterogeneous lesions in the pelvis and irregular capsular swelling. Hematological test results revealed: hemoglobin 10.0 g/dL, white blood cells 6.550/μL, CD4+ cells 188/μL, and platelets 235.000/μL. Serum test results revealed: albumin 1.9 g/dL, aspartate aminotransferase (AST) 42 U/L, lactate dehydrogenase (LDH) 804 U/L, BUN 24 mg/dL, creatinine 2.02 mg/dL, uric acid 13.9 mg/dL, C-reactive protein (CRP) 9.88 mg/dL, and soluble IL2-receptor 1540 U/mL. Urinalysis demonstrated a protein level of 0.21 g/dL; microscopically there were a few epithelial cells and casts. Bone marrow testing showed 12.6% abnormal, large convoluted cells with CD10+, 19+, and 20+ according to both immunohistochemistry and flow-cytometry (FCM) (**Figure 1A**). Serological tests for viruses showed HBV surface antigen (HBsAg) >2000 (IU/mL), surface antibody (HBsAb) <0.1, core antibody (HBcAb) 100, HBV DNA (TaqMan PCR) 8.7 log copy/mL, HIV Ab positive, and HIV-RNA real-time polymerase chain reaction (PCR) 1.5 x 10^4 copy/mL. Analysis of HBV genotype revealed mixed infections with genotype A/E by hepatitis B genotyping EIA kit [18]. The patient's wife and two children exhibited history of acute HBV hepatitis 10 years ago. The left testicular tumor was completely removed, and finally, he was diagnosed with features intermediate between

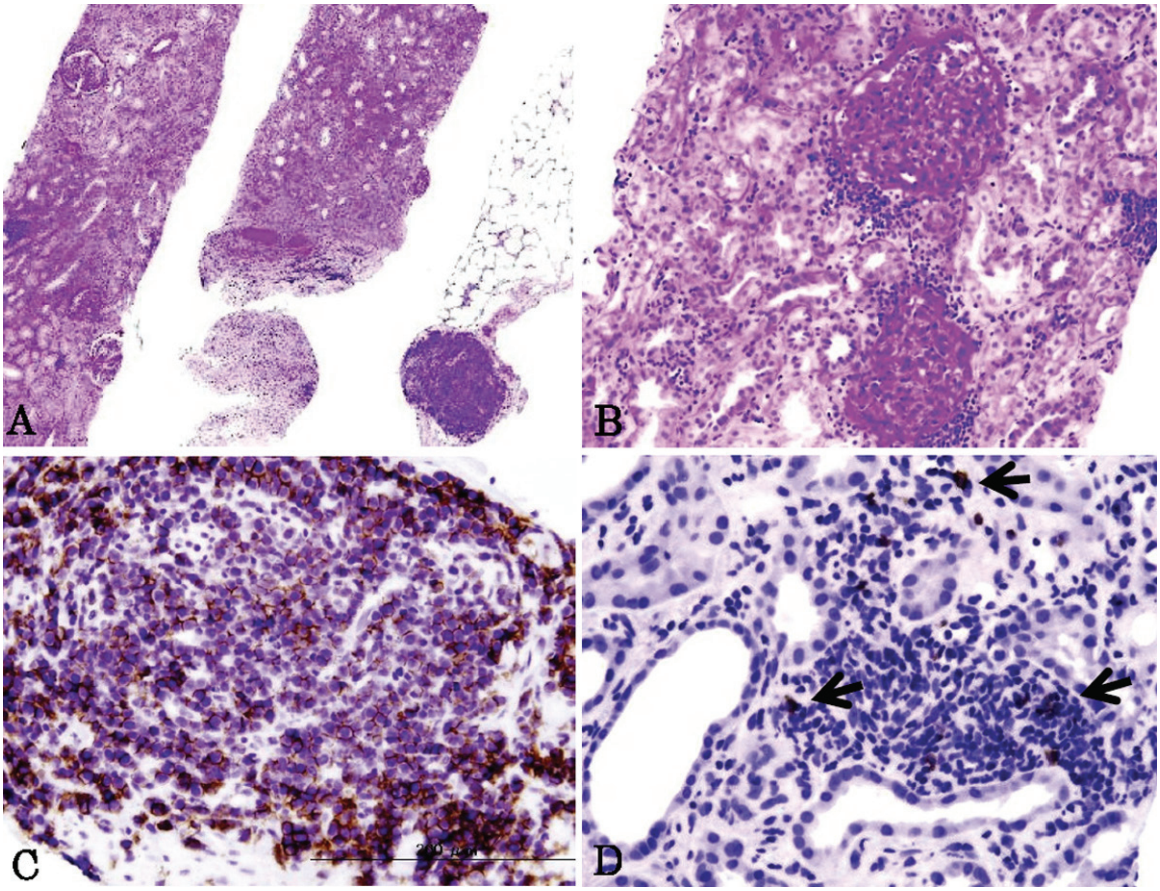

Figure 2. Renal biopsy specimen (Pas stain). A. Three biopsy specimen. Right side specimen shows renal subcapsule. B. Interstitial infiltration of mononuclear cells. CD 20 immunostaining of renal specimen. C. Large cells in aggregation are positive for CD 20. D. A small number of cells in the interstitium are positive for CD 20 (arrows).

diffuse large B-cell lymphoma and Burkitt lymphoma (**Figure 1B**). A needle biopsy of the right kidney exhibited atrophy and hydro-degeneration of renal tubules, interstitial mild inflammatory cells as small lymphocytes, neutrophils, and plasma cells; and in sub-capsule, a few large lymphoid cells without glomerular lesions (**Figure 2A-D**). He developed acute kidney injury (AKI) with elevated serum creatinine up to 6.33 mg/dL. Following his definite diagnosis, he was immediately treated with combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone: CHOP) with prophylactic intrathecal (IT) injection (methotrexate (MTX) 15 mg/cytarabine 40 mg (AraC), and concomitantly received combined anti-retrovirus therapy (cART: emtricitabine/tenofovir/efavirentz/nerfinavir) with prophylactic therapy as fluconazole (FCZ) 400 mg/day and sulfamethoxazole/trimethoprim (ST) 160/800 mg/day. Cerebrospinal fluid (CSF) exhibited a protein level of 43 mg/dL and cells <1. Following initiation of CHOP therapy, all of his symptoms and renal function immediately improved. His LDH and CRP dramatically decreased to 324 U/L and 0.3 mg /dL. However, 20 days after the first cycle of CHOP, he developed pneumonia, which was suggested to be caused by some virus on CT. There was no evidence of regrowth of lymphoma or underlying infectious agents despite extensive examinations. His laboratory data were normal aside from elevated CRP (3.45 mg/dL). His CD4+ count increased significantly and reached 598 cells/μL (CD3+ 1441 cells/μL), HIV RNA decreased to 5.1 x 10^1 copy /μL, and HBV DNA remained at a log copy level of 6.2. The second cycle of CHOP was initiated with prophylactic IT, and thereafter he quickly, spontaneously recovered from pneumonia without additional anti-fungal or anti-bacterial treatment. His CRP decreased to 0.57 mg/dL, and LDH remained unchanged. These findings suggest that his pneumonia was an inflammatory immune reconstitution syndrome (IRIS);

the underlying infectious agents were not identified. Eighteen days after the second cycle of CHOP, he developed headache and left ptosis. Brain magnetic resonance imaging (MRI) showed patchy high signal intensity lesions in the white matter on FLAR images without any abnormal findings in the oculomotor nerve, trigeminal nerve, optic nerve, or cavernous sinus. CSF exhibited protein of 64 mg/dL, 1 cell/μL, and no specific clonal B-cells by FCM. Viral PCR, including cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella zoster virus (VZV) were all negative in his CSF. His CD4+ count showed 261 cells/μL and HIV RNA below 4.0 x 10^1 copy/μL. We could not determine whether his neurological symptoms were caused by infiltration of lymphoma cells or due to infectious agents or not. In addition, we also completely did not deny neuroIRIS in his central nervous system (CNS). After deliberation, we decided to administer B course of high-dose chemotherapy (A course: cyclophosphamide, vincristine, doxorubicin, dexamethasone, B course: MTX 1000 mg/m^3, AraC 3000 mg/m^3 x2: hyper-CVAD/MA) to the patient. Thereafter, his neurological symptoms gradually improved, and the patient received four cycles of hyper-CVAD/ MA chemotherapy with cART. After completion of chemotherapy courses, the CD4+ count was 436 cells/μL and the HIV RNA viral load dropped to undetectable levels; HBV DNA was 2.6 log copy/μL. A repeat MRI scan showed no marked changes of white matter lesions. He was well, and continued to be treated with cART without reactivation of HBV, and without adverse effects.

Discussion

Coinfection with HBV and HIV are common globally; the estimated prevalence is 7-11% [19, 20]. HBV genotypes exhibit distinctive geographical distribution [6-8]. HBV genotype A and D are predominant in Europe and North America, B and C in East Asia, D in North Africa, E in West Africa, and F and H in Latin America [21]. In Japan as East Asia, HBV has principally spread through mother-to-child infection; its genotypes C (85%) and B (12%) are primarily native to Japan [18]. In a recent report of HBV genotypes co-infected with HIV in Japan, genotype A (80%) and C (19%) were predominant and were postulated to be transmitted by sexual contact [22]. These prevalent developmental changes in HBV genotypes in HIV carriers indicate that universal vaccination for juveniles against HBV in Japan is warranted. Our patient exhibited mixed genotypes HBV (A/E). To the best of our knowledge, this is the first combined genotype A and E carrier co-infected with HIV. A recent report from Sri Lankan revealed a high proportion of mixed genotype infections among B, C and D [20]. In another report from Laos, HBV mixed infections led to frequent recombinations in the same donor [19]. However, there are no previous reports concerning HBV genotypes not only in HAL but also in malignant lymphoma. Therefore, the associations among HBV genotypes, development, characteristics, and chemosensitivity of HAL remain unknown. These issues should be addressed in future large scaled-studies.

HIV-associated AKI is clinically, etiologically, and morphologically divers [11]. The histological findings in our renal biopsy specimen are compatible with acute interstitial nephritis (AIN). In previous reports, pathogenetic factors involved in AIN with HIV infection are drugs, such as NSAIDs and antiretroviral drugs, IRIS, and infections including HIV itself [11-13]. Possible pathogenetic factors in our case were NSAIDs or HIV or both because he was treated with NSAIDs for one month and rapidly recovered from AIN concomitantly with cART. Although the biopsy specimen did not exhibit a diffuse infiltration of lymphoma cells into the renal cortex or a small number of cells in the renal interstitium, but clusters of lymphoma cells in the sub-capsule, we could not dismiss the contribution of lymphoma to renal dysfunction. In general, involvement of lymphoma in the kidney is morphologically classified as interstitial type or intra-glomerular type, and the interstitial infiltration type shows minimal proteinuria and bilateral enlargement of the kidneys on imaging [13, 15]. In our case, in addition to enlargement of the kidneys, the CT showed low or heterogeneous lesions in the pelvis and irregular capsular swelling lesions. These findings suggest that a number of lymphoma cells potentially infiltrated the kidney in our case. Moreover, the clinical course that the enlargement of the kidneys resolved within a few days after chemotherapy suggests lymphoma as a potential cause of AKI. Thus, we could not eliminate the possibility of sampling error in our case. We hypothesized that in an early

phase of AKI, NSAIDs or HIV or both may play a major role in renal dysfunction, and in the later phase, lymphoma may play a role in renal impairment. Treatment of AKI primarily depends on the pathogenic factors. However, we could not determine which factors were dominant or concomitant in this patient's renal dysfunction before initiation of treatment. Fortunately, the drugs administered for the treatment of HAL combatted the postulated pathogenetic factors of AKI in our case. However, we did not detect any infectious agents inducing AKI, except for HIV itself.

IRIS is a well-known complication in HIV-infected patients after cART, but uncertainty exists with regards to its pathogenesis, management, and definition [23, 24]. A number of case definitions for IRIS have been proposed [16], but there is no gold standard definition of IRIS. Even so, the minimum criteria are; 1) temporal association between cART and subsequent development of symptoms, 2) evidence of immune restoration by a decrease in HIV-RNA level by more than 1 log copy/mL and an increase in CD4+ count from baseline, and 3) existence of clinical symptoms and signs consistent with inflammatory process. The immunopathogenesis of IRIS is unclear, but is believed to result from a dysregulated immune response to various antigenic stimuli including innate antigens as well as infectious organisms after cART. In our case, pneumonia following the first cycle CHOP with cART fulfilled the described minimum criteria of IRIS, although underlying infectious agents were not detected. His pneumonia rapidly resolved after the second cycle of CHOP (including prednisolone). Therefore, these clinical improvements potentially reveal the efficacy of prednisolone for IRIS presenting with pneumonia. In general, the majority of patients with IRIS exhibit a self-limiting disease course. Thus, management of IRIS relies on watchful observation. However, the incidence of IRIS during treatment of HAL remains unknown. There have been only two previous reports of IRIS with HAL [16, 17]. They said that IRIS should be differentiated from relapse or regrowth of HAL, and that it may be difficult for physicians to make the differential diagnosis [16, 17, 23, 24]. We suggest that a number of cases of IRIS may develop during treatment for HAL, but may be frequently overlooked because of spontaneous improvement.

The patient developed ptosis due to the left oculomotor and abducens nerve palsy. It was difficult to determine the pathogenesis of the patients' neurological symptoms, especially to differentiate possible pathogens from lymphoma or others. In previous studies, a 3-8% incidence of ocular nerve palsy in patients with HIV infection was reported [25, 26]. In one report, toxoplasmosis and cryptococcosis were the most commonly detected pathogens inducing palsy, but HIV itself was not excluded [25]. In our case, extensive examinations did not detect any presumed pathogens in his CNS. He had been always treated with FCZ and ST as prophylactic agents for toxoplasmosis and cryptococcosis. Furthermore, his palsies gradually improved without any additional specific infectious therapies. These clinical course and laboratory findings suggest that infectious pathogens were unlikely to induce his cranial nerve palsies. In recent reports, 10-20% of lymphoma patients with HIV-infection had meningeal involvement [27, 28]. The incidence rate of meningeal involvement may rely on the methods of evaluation [27]. In our case, repeated CSF studies by FCM exhibited only mild protein elevation, and detected no specific monoclonal B-cell population in his CSF. His systemic manifestations, except for palsies, remained stable or slowly improved, and moreover, the laboratory findings improved; thus, his lymphoma appeared not to relapse. Previous reports have suggested that all patients with HIV-infection lymphoma receive IT for prophylaxis of CNS involvement [1, 2], and demonstrated that the incidence rate of CNS involvement decreased by combination with cART [29]. We treated the patient with both prophylactic IT and cART. Although it was unclear whether he responded to high-dose chemotherapy including MTX and AraC, known to easily penetrate the CNS wall, his neurological symptoms eventually, gradually improved. In our case, a repeat brain MRI showed patchy high signal intensity lesions in the white matter, but no gadolinium-enhancing lesions in the left oculomotor nerve. The gold standard of diagnosis for leptomeningeal lymphoma is both CSF cytology and FCM [2]. On the other hand, MRI imaging exhibited positive findings in only 50% of patients with CNS involvement of lymphoma [30]. However, false negative MRI could not be excluded in our case. NeuroIRIS was less likely to induce ptosis in our case because of the obscure causal associa-

tion between cART and its onset, or no evidence of inflammatory reactions by brain MRI [31].

In conclusion, we report the first case of mixed HBV genotypes (A/E) with AKI, IRIS, and left-ptosis in HAL. We suggest that this study may be valuable in assessing HBV genotypes in lymphoma; our case study indicates that it is possible to identify the characteristics between a specific HBV genotype and lymphoma, and to provide the most appropriate treatment for lymphoma patients co-infected with HBV.

Conflict of interest

Nothing to report.

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