

Four Cases of Non-Hodgkin's Lymphoma in AIDS patients

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The incidence of opportunistic infection has decreased since the introduction of highly active antiretroviral therapy, so lymphoma is now far and away the most lethal complication of acquired immunodeficiency syndrome. We have experienced four cases of NHL in AIDS patients. The first patient was a 37 year old male who presented with left sided hemiplegia due to CNS lymphoma. The second patient was a 40 year old male who was admitted because of jaundice; he was diagnosed as having lymphoma that exclusively involved the liver. The third patient was a 38-year-old male who presented with palpable mass in the left cervical region, which was diagnosed as lymphoma. Above three cases were confirmed as diffuse large B cell lymphoma. The fourth patient presented with a protruding swollen chest wall mass on the right side of his chest, this was determined pathologically to be the Burkitt's type. The latter case is the first report of NHL involving the chest wall musculature in a Korean AIDS patient.

Key Words : Human Immunodeficiency Virus, Acquired Immunodeficiency syndrome, Non-Hodgkin's Lymphoma

INTRODUCTION

After the discovery of acquired immunodeficiency syndrome (AIDS) in the U.S.A in 1981¹⁾, the incidence of human immunodeficiency virus (HIV) infection has been rapidly expanding. A year later, the first case of non Hodgkin lymphoma (NHL) was reported in an AIDS patient. NHL has been included as an AIDS-defining illness since 1985²⁾. The number of those people infected with HIV has now reached nearly 40 million world-wide as of December 2004³⁾. The first case of HIV infection of a foreign resident was reported in Korea in June 1985; the number of people infected with HIV has been steadily rising each year and it reached 3,294 as of March 2005, based on the report of the Korean National Institute of Health. The disease is widely dispersed throughout the entire world, and the HIV infection rate of our country is currently classified as a very low stage along

with other countries such as Japan and the Philippines. However, with the explosive increase of the number of patients with AIDS in countries such as China, Indonesia and Vietnam, it seems Korea can not long remain categorized as a safe place⁴⁾.

The current study reports on four cases of NHL that developed in Korean AIDS patients. It is very intriguing observation that all four cases of AIDS related lymphoma were detected at different anatomical site of the body, and thus, the patients displayed different clinical symptoms at their initial presentation. According to our observations, it's highly recommended that physicians should pay more attention to any single mass lesion in AIDS patients and there should be the suspicion of possible lymphomatous involvement. This can help achieve early detection of the drastic complications of AIDS and so there is a fighting chance to induce remission of disease. We

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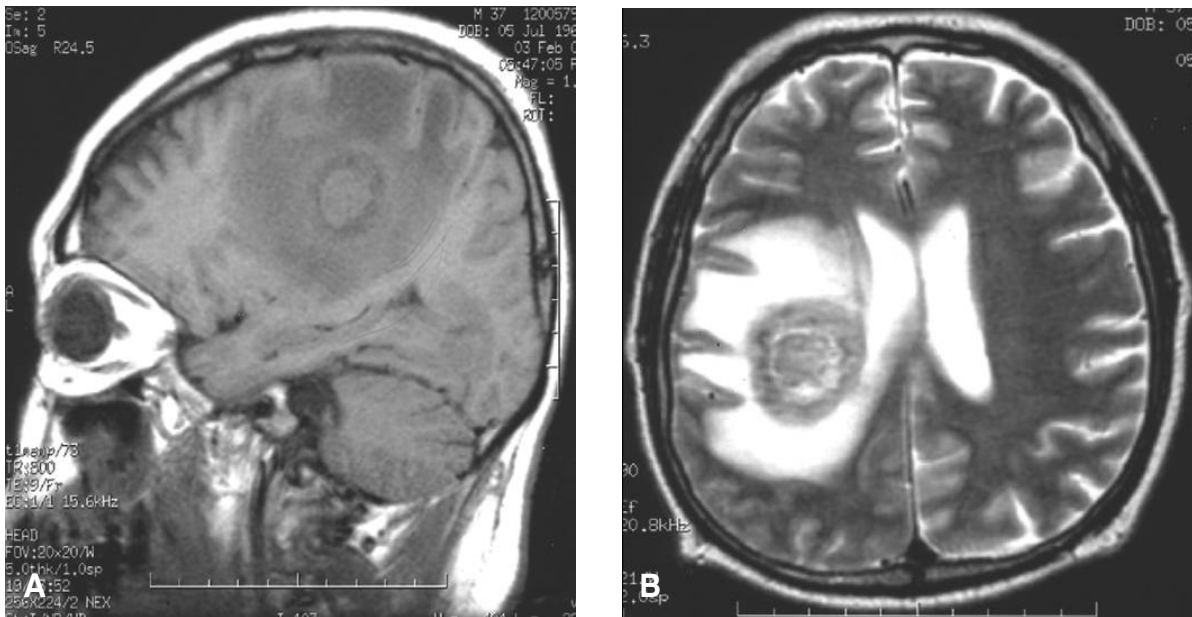


Figure 1. (A) Brain MRI shows a 4cm sized round mass involving the right frontal lobe. (B) The T2 weighted image shows extensive areas of perilesional edema involving the right frontoparietal region and there is a mass effect upon the right lateral ventric

report here on lymphoma in Korean AIDS patients, and these patients presented with their own distinct clinical features at presentation. We also include a review of the relevant medical literature.

CASE REPORT

Case 1

A 37-year-old male was admitted to our hospital because of his left sided hemiplegia that he had experienced for 3 months. He was known to be positive for HIV, as was determined during evaluation for idiopathic thrombocytopenic purpura in a foreign country about 6.5 years before this admission. At that time, he had been treated with zidovudine, lamivudine and saquinavir for the management of AIDS for 9 months and then he discontinued therapy of his own will. He was advised to restart treatment with zidovudine, lamivudine and indinavir at our hospital 4 years ago. He noticed weakness on the left side of his body during movement, which had slowly progressed and he finally developed left-sided hemiplegia 3 months previously. At the time of admission, he had complaints of headache and night sweats. He was diagnosed as having idiopathic thrombocytopenic purpura about 6.5 years ago and so splenectomy was done. Even after splenectomy, the thrombocytopenia continued. He was treated with steroid, vincristine, intravenous gammaglobulin, rituximab and danazole. He had also experienced liver abscess 4 years ago. He had

received radiation for Kaposi sarcoma about 8 months before admission. On admission, the blood pressure was 90/60 mmHg, the pulse rate 100/min, the respiration rate 22/min and the body temperature was 38°C. Upon physical examination, the patient was in poor general condition with anemic conjunctiva. There were no signs of hemorrhagic diathesis or icterus. The laboratory findings were as follows: hemoglobin 7.4 g/dL, WBC 8,300/mm³ (neutrophils: 79.5%, lymphocytes: 14.6%, monocytes: 4.6%), platelets 10,000/mm³, erythrocyte sedimentation rate (ESR) 2 mm/h, AST 24 IU/L, ALT 9 IU/L, total bilirubin 0.7 mg/dL, LDH 473 IU/L, protein 3.9 g/dL, albumin 2.3 g/dL, BUN 9.5 mg/dL, creatinine 0.42 mg/dL, calcium 7.3 mg/dL, phosphorus 3.1 mg/dL, Na 130 mmol/L, K 3.0 mmol/L, the total number of CD4 and CD8 T lymphocytes was 46/mm³ and 621/mm³, respectively, and the ratio of CD4/CD8 was 0.07. The chest X-ray was not remarkable. Brain MRI (Figure 1A) shows 4 cm-sized round mass involving the right frontal lobe. The T1 weighted image and the T2 weighted image (Figure 1B) showed extensive areas of perilesional edema involving the right frontoparietal region and there was a mass effect upon the right lateral ventricle. Stereotactic biopsy of the brain lesion was performed, and histological examination disclosed atypical lymphoid cells with a predominant perivascular arrangement (Figure 2). Immunohistochemical examination showed positivity for CD20. The diagnosis of diffuse large B-cell lymphoma involving the CNS was made. The patient was treated with brain radiation. Sadly, he died of pneumonia 13 days after brain radiation therapy.

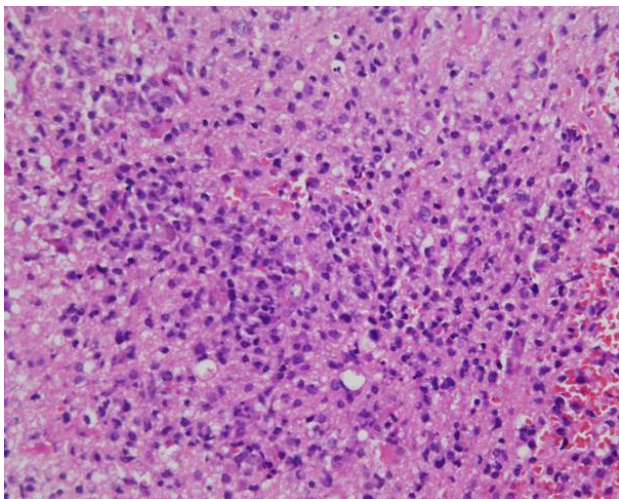


Figure 2. The microscopic findings of the mass show diffuse proliferation and infiltration of atypical large lymphocytes, and lymphoma cells are distributed along the vascular channels as perivascular cuffs (H&E stain, x400)

Case 2

A 40-year-old man was hospitalized due to jaundice and lethargic fatigue that started 10 days prior to admission. The patient had complaints of weight loss and night sweats. Four months prior to this admission, he had visited to the Department of ENT at another hospital with the complaint of nasal stuffiness. At that time, the serologic testing for hepatitis B antigen and anti-HIV antibody were positive. He has been treated with zidovudine, lamivudine and efavirenz for two months until admission. He assumed that his AIDS was transmitted from heterosexual contact at abroad ten years ago. On admission, the blood pressure was 120/70 mmHg, the pulse

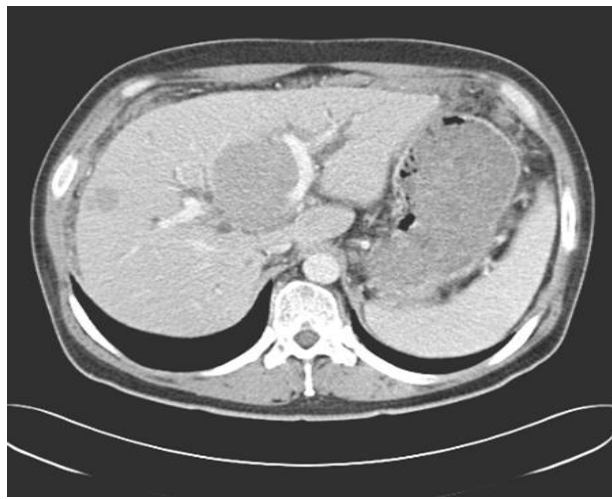


Figure 3. Abdomen CT shows multiple variable sized homogenous hypodense masses in both hepatic lobes.

rate 90/min, the respiratory rate 20/min and the body temperature was 36.6°C. He was icteric on the physical examination. The liver was tender and firm in consistency. It was palpated at a three-finger breadth below the right costal margin. His spleen and lymph nodes were not enlarged. The laboratory results were normal apart from an ESR of 120 mm/h; leukopenia 3,930/mm³ (neutrophils: 58.8%, lymphocytes: 31% and monocytes: 8.4%) and hemoglobin 9.4 g/dL. The liver function tests were abnormal: total bilirubin 8.9 mg/dL (direct bilirubin: 6.05 mg/dL), AST 171 IU/L, ALT 100 IU/L and LDH 1063 IU/L. The total number of CD4 and CD8 T lymphocytes was 290/mm³ and 568/mm³, respectively, and the ratio of CD4/CD8 was 0.51. Abdominal enhanced CT scanning revealed

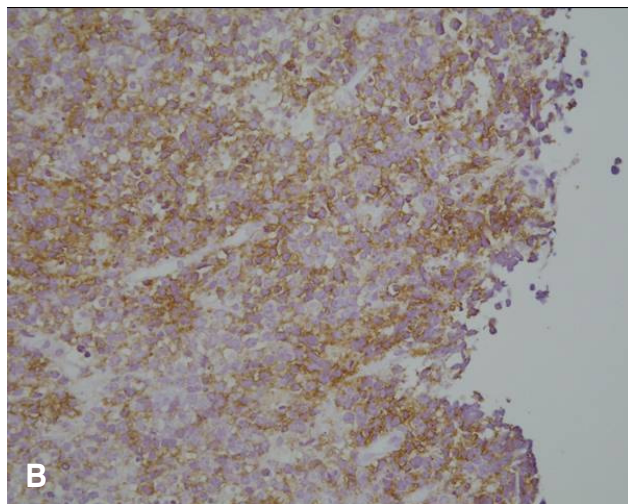
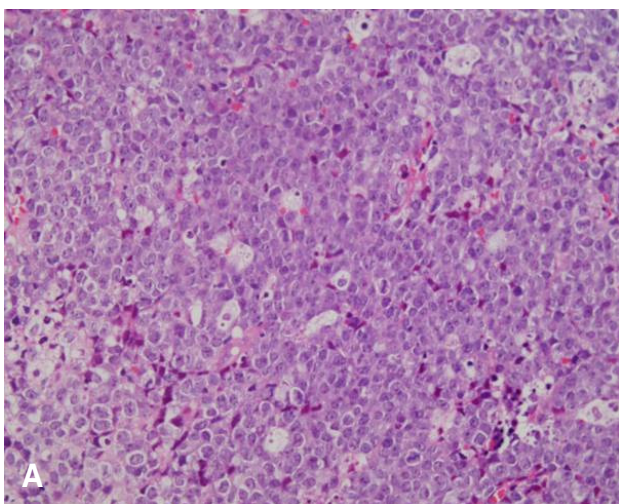


Figure 4. (A) The microscopic findings of the mass show a diffuse proliferation of large pleomorphic cells that contain abundant cytoplasm and large, round nuclei (H&E stain, x400). (B) Immunohistochemical staining shows CD 20 positivity (x400).

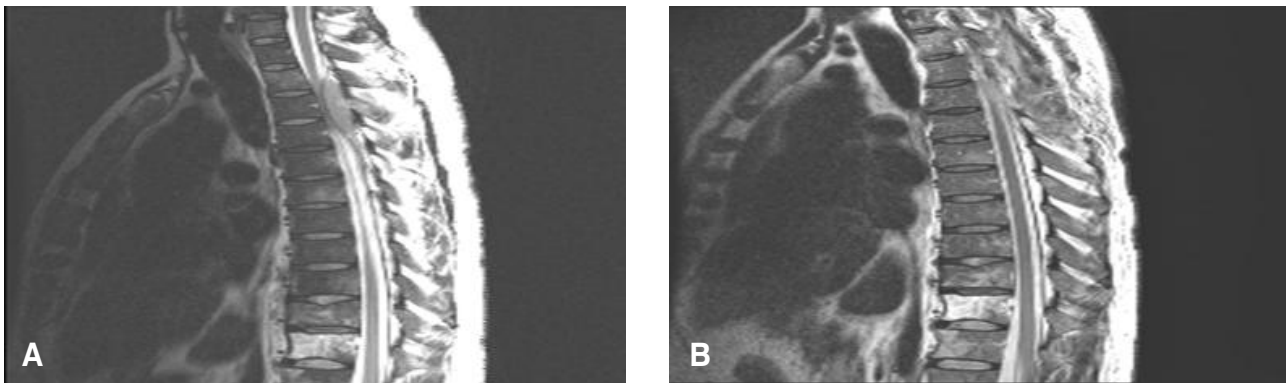


Figure 5. (A) The initial D-spine MRI shows the signal intensity of the entire vertebral body is diffusely decreased with heterogeneous enhancement at the D9 to D11 vertebral bodies after gadolinium injection. An elongated posterolateral epidural mass is seen at the D2 through D4 levels, which causes severe cord compression. (B) After radiotherapy and chemotherapy, the follow up MRI revealed marked regression of epidural mass and cord compression at the D2-4 level.

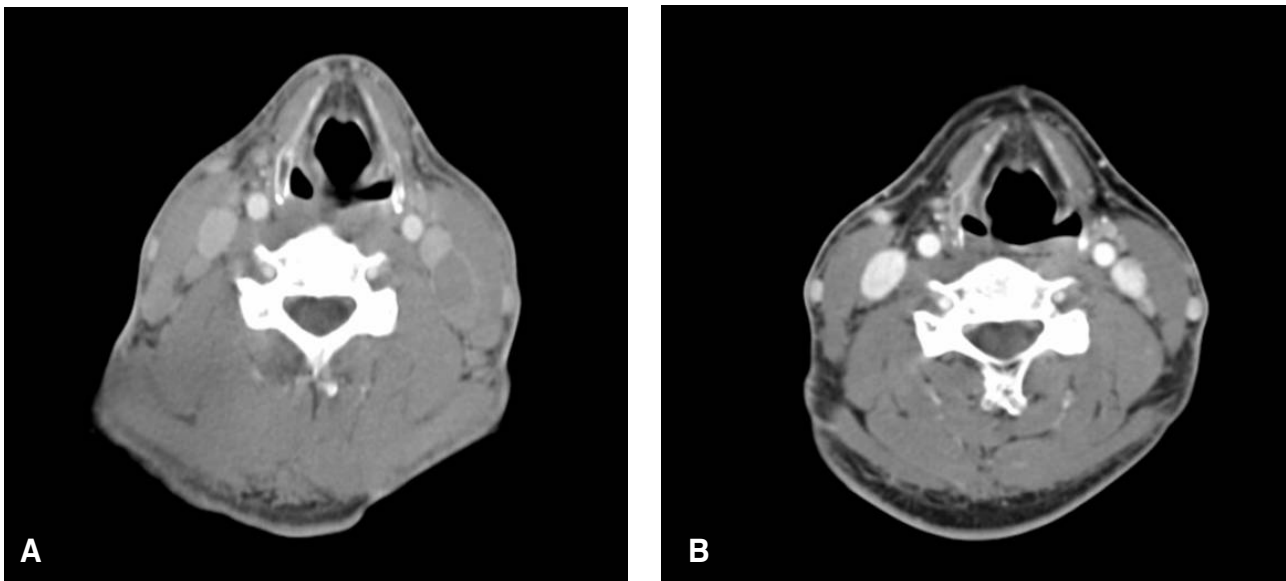


Figure 6. (A) CT scan of the head and neck shows the enlarged left sided cervical lymph nodes that measured 1.6cm x 2.4cm in diameter. (B) After 6 cycles of R-CHOP, the follow-up CT revealed marked regression in the size of lymph nodes in both internal jugular channels.

multifocal and variable sized homogenous hypodense masses in both hepatic lobes (Figure 3). A liver biopsy showed a heavy infiltration composed mainly of large lymphoid cells (Figure 4A). Immunohistochemical staining revealed the atypical cells to be CD20 positive (Figure 4B), which established a diagnosis of diffuse large B-cell lymphoma according to the WHO classification. Bone marrow biopsy demonstrated normal cellularity with normal maturation of all three cell lines. There was no malignant cell infiltration. After the patient was diagnosed as having diffuse large B-cell lymphoma, he received VAD (vincristine 0.4 mg, adriamycin 9 mg/m², dexamethasone 40 mg on days 1-4, and additional dexamethasone on days 9-12 and days 17-20). The

patient seemed to show a little clinical improvement, but before starting the second chemotherapy, he developed signs of spinal cord compression (Figure 5A). Emergency radiation therapy was delivered to the spine lesion. CHOP chemotherapy (cyclophosphamide 750 mg/m², adriamycin 50 mg/m² and vincristine 1.4 mg/m² on day 1 and prednisone 100 mg/m² on days 1-5) and laminectomy induced temporary improvement (Figure 5B). Alas, the paraplegia continued and his clinical condition progressively worsened. He passed away 103 days after starting the second round of chemotherapy from complications of pressure sores, deep vein thrombosis and pulmonary thromboembolism.

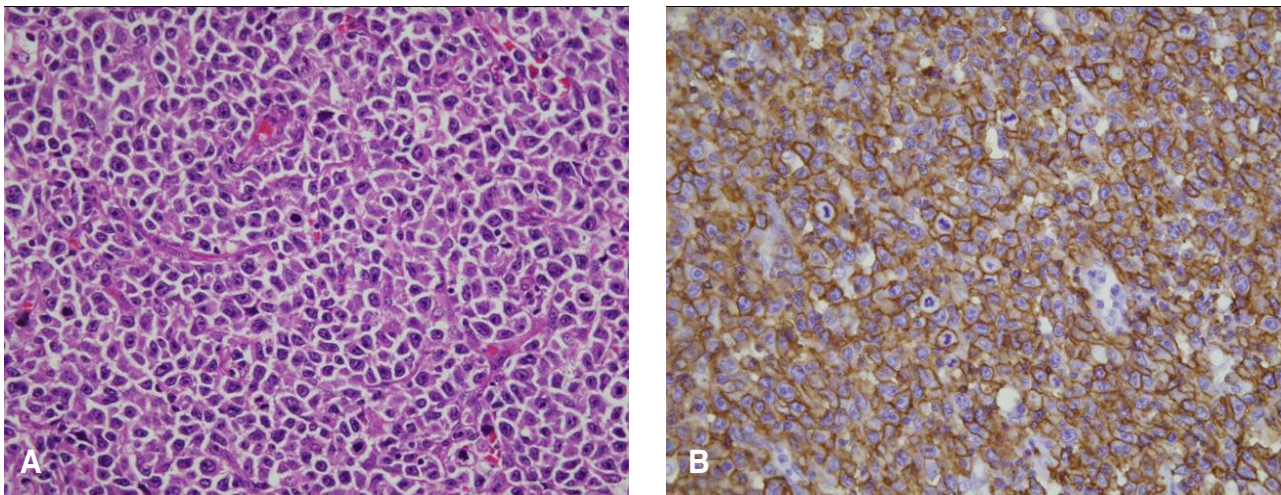


Figure 7. (A) Microscopic findings of the mass show a diffuse proliferation of large pleomorphic cells (H&E stain, x400). (B) Immunohistochemical staining shows CD 20 positivity (x400).

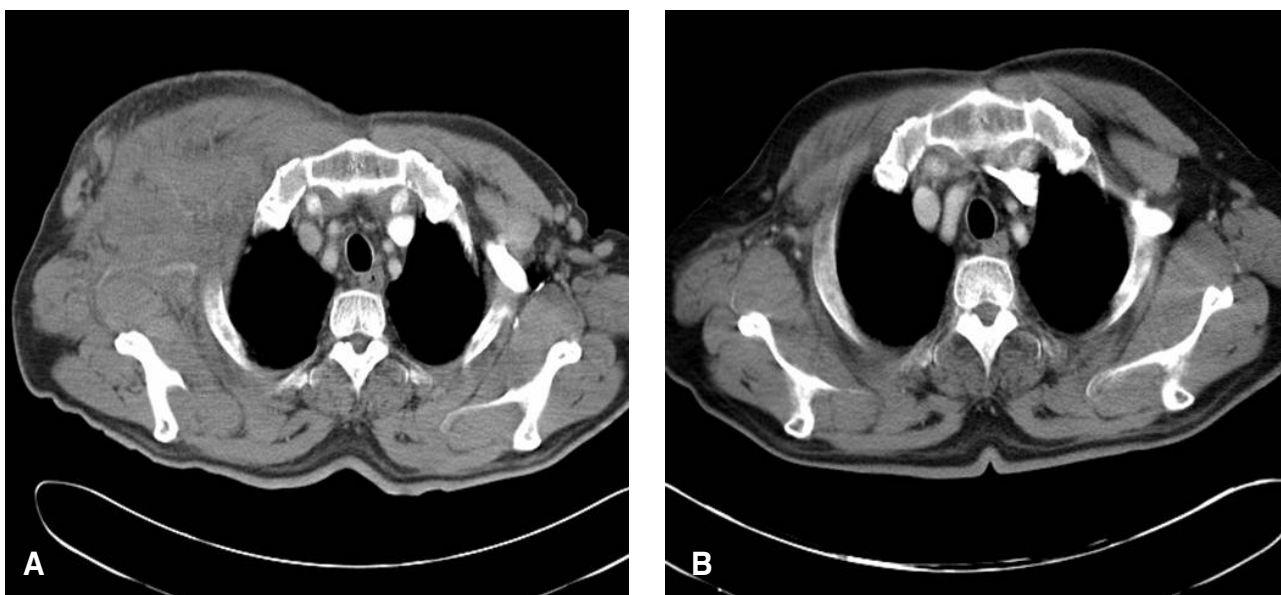


Figure 8. (A) The initial chest CT shows extensive heterogeneously infiltrative lesions involving the right side of the chest wall musculature with the accompanying edematous changes of the overlying skin and subcutaneous layer. (B) After 4 cycles of chemotherapy, the follow-up MRI revealed marked regression of the lymphoma in the right chest wall.

Case 3

A 38-year-old male with AIDS presented with a palpable mass he'd had for 5 months in the left cervical region. HIV infection was possibly through heterosexual contact and he was diagnosed two years earlier, but no particular treatments were established before admission. On physical examination, 0.8 cm-sized lymph nodes were palpable in the left cervical areas. The heart and lungs were normal, and the chest X-ray was normal. A CT scan of the head and neck (Figure 6A) showed enlarged left sided cervical lymph nodes that measured 1.6 cm x 2.4 cm

in diameter. Excisional biopsy of a cervical lymph node was performed, and the histologic study suggested diffuse large B-cell lymphoma (Figure 7A). Immunohistochemical staining showed the atypical cells to be CD20 positive (Figure 7B). On admission, the patient did not declare any discomfort and the physical examination was normal. The laboratory findings were as follows: hemoglobin 14.4 g/dL, WBC 5,310/mm³ (neutrophils: 55.9%, lymphocytes: 39% and monocytes: 4.1%), platelet 178,000/mm³, ESR 9 mm/h, AST 39 IU/L, ALT 32 IU/L, total bilirubin 1.5 mg/dL, LDH 378 IU/L, protein 7.9 g/dL, albumin 4.0

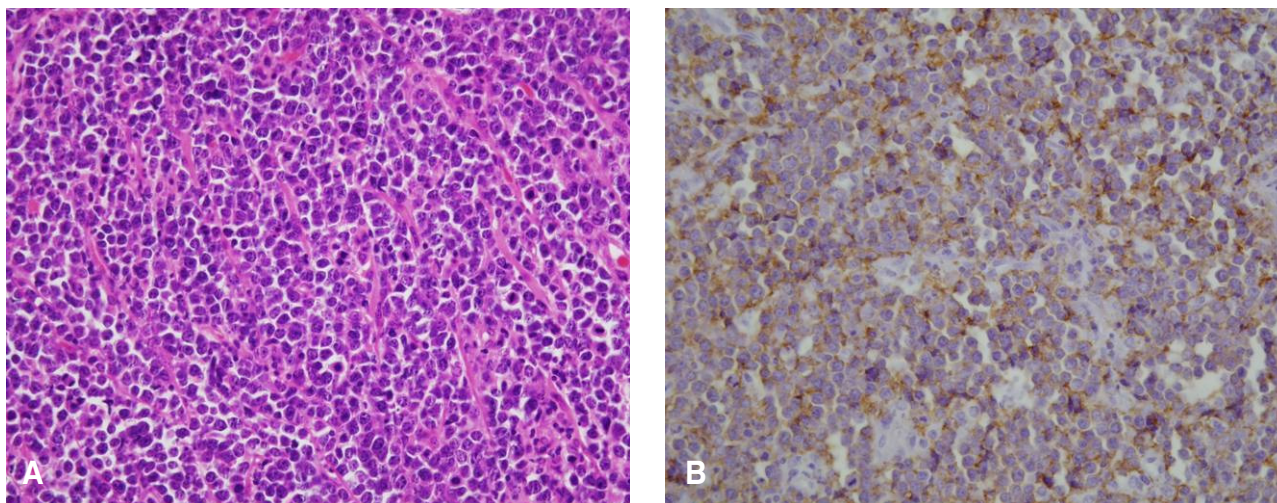


Figure 9. (A) Microscopic findings of the mass show a starry-sky pattern with diffuse proliferation of small to medium sized neoplastic cells (H&E stain, x400). (B) Immunohistochemical staining shows CD20 positivity (x400).

g/dL, BUN 15.9 mg/dL, creatinine 0.88 mg/dL, calcium 8.5 mg/dL, phosphorus 4.2 mg/dL, Na 137 mmol/L, K 4.5 mmol/L, the percent of the CD4 and CD8 T lymphocytes was 20.5% and 70% of the total lymphocyte count, respectively, and the total number of CD4 cells was $420/\text{mm}^3$. The CD4/CD8 ratio was 0.36. He was treated via immunochemotherapy with Rituximab and CHOP for six cycles. After 5 cycle of R-CHOP, the CD4 cell count decreased from 420 to $95/\text{mm}^3$ and a regimen of zidovudine, lamivudine and didanosine were used as HAART. After 6 cycles of R-CHOP, the follow-up CT revealed marked regression in the size of the lymph nodes at both internal jugular channels (Figure 6B). He is currently under follow-up for the lymphoma.

Case 4

A 67-year-old male was admitted to our hospital because of a protruding swollen chest wall mass on his right side, and he had noticed this mass for 1 month. He also had a complaint of night sweats. His past medical history included an electrical burn about 30 years ago and herpes zoster four months prior to this admission. Serological HIV positivity was detected four months ago while he was being treated for his herpes. His HIV infection was assumed to be transmitted through blood transfusion. He denied ever having homosexual contact or drug abuse. He was on zidovudine, lamivudine and lopinavir. On admission, his blood pressure was 120/80 mmHg, the pulse rate 68/min, the respiration rate 18/min and the body temperature was 36.2°C . The patient appeared generally well on physical examination. The heart and lungs sounds were normal. A chest wall mass measuring 15 cm x 18 cm in diameter was palpable on the right side of his chest. The laboratory finding were as follows: hemoglobin 12.2 g/dL, WBC $6,990/\text{mm}^3$ (neutrophils: 36.5%, lymphocytes: 52.5% and monocytes: 8.9%), platelets

$131,000/\text{mm}^3$, ESR 8 mm/h, AST 37 IU/L, ALT 22 IU/L, total bilirubin 0.55 mg/dL, LDH 2,024 IU/L, protein 6.5 g/dL, albumin 3.5 g/dL, BUN 13.7 mg/dL, creatinine 1.2 mg/dL, calcium 7.6 mg/dL, phosphorus 3.4 mg/dL, Na 139 mmol/L, K 4.3 mmol/L, the total number of CD4 and CD8 T lymphocytes was $317/\text{mm}^3$ and $3,085/\text{mm}^3$, respectively, and the ratio of CD4/CD8 was 0.1. The chest X-ray was unremarkable except for marked soft tissue swelling of the right chest wall. The initial chest CT (Figure 8A) showed extensive heterogeneously infiltrative lesions that involved the right side of the chest wall musculature with accompanying edematous change of the overlying skin and subcutaneous layer. The microscopic finding of the mass showed a starry-sky pattern with diffuse proliferation of small to medium sized neoplastic cells (Figure 9A). Immunohistochemical examination showed positivity for CD20 (Figure 9B). The pathological diagnosis was Burkitt's lymphoma. The patient received 4 cycles of dose adjusted EPOCH regimen (a 4-day infusion of etoposide $50 \text{ mg}/\text{m}^2$, doxorubicin $10 \text{ mg}/\text{m}^2$ and vincristine $0.4 \text{ mg}/\text{m}^2$ with dose-adjusted cyclophosphamide $375 \text{ mg}/\text{m}^2$ on day 5 and prednisone $60 \text{ mg}/\text{m}^2$ for 5 days) every 3 weeks. Granulocyte colony-stimulating factor was used uniformly, beginning at day 6, and all HAART was withheld until day 6 of the last dose of chemotherapy. The soft tissue lesion responded very well to chemotherapy. The chest wall mass decreased in size after the first cycle of chemotherapy. After four cycles of chemotherapy, follow-up CT revealed marked regression of the lymphoma in the right chest wall (Figure 8B). He is currently alive and well in a state of complete remission of the lymphoma for more than 18 months.

DISCUSSION

Lymphoma is considered a late manifestation of HIV infection and it remains the second most common malignant complication, after Kaposi's sarcoma, for patients suffering from HIV infection. AIDS related lymphoma appears to be slightly more common in hemophiliacs and less common in intravenous drug users as compared with the other HIV transmission groups⁵.

The incidence of NHL in AIDS patients is approximately 3.0~3.6%, which is 60~100-fold more than the risk of developing NHL for the general population. The risk of developing lymphoma in patients with symptomatic HIV infection appears to be approximately 1.6% per year^{5,6}. The patients with HIV related lymphoma are younger than those patients who have HIV negative lymphoma. The incidence of high grade lymphoma is 15~20% in the general lymphoma population as compared with 80% for the AIDS-related lymphoma, and the AIDS-related lymphomas show a high incidence of extranodal involvement^{2,5,7}. The most common sites of involvement are the CNS (26%), bone marrow (22%), the gastrointestinal tract (17~25%) and liver (12%)^{8,9}.

The exact pathogenesis of AIDS-related lymphomas is not fully understood. One factor may be the immune suppression itself. Chronic antigenic stimulation of the B lymphocytes by antigens, mitogens or viruses, including Epstein Barr virus (EBV) and HIV, play a role, but the continued HIV viral burden on B cells, in association with EBV and Herpes simplex virus 8 (HHV-8), is also believed to play a role. Immunosuppression and EBV infection favor the expansion of B cell clones, thereby allowing proliferation of the clones of cells that have undergone alterations of their oncogenes or tumor suppressor genes¹⁰. EBV has been pathogenetically associated with the development of AIDS related lymphoma. Approximately 30~50% of NHL seems to be related to EBV infection, and only 25~40% of Burkitt's lymphomas were EBV-positive as compared to 79% of the immunoblastic or large cell lymphomas¹¹. Genetic alterations play an important role not only in the pathogenesis of lymphoma, but also in determining the histology of the resulting clonal proliferation. In close to 60% of Burkitt's lymphomas, this is compounded by mutations in the p53 tumor suppressor gene that result in the deregulation of apoptosis. C-myc rearrangement and p53 mutations occur more frequently in the Burkitt's lymphoma; in over 70% of ARL, there are mutations that result in deregulation of the BCL-6 proto-oncogene⁸.

HAART was introduced to the developed countries at the end of 1996. In the pre HAART era, the incidence of AIDS-related lymphoma remained fairly constant at around 6~7 cases per 1000 person-years. NHL accounted for only 1.5% of first AIDS defining illnesses, but it rose from 3.0~3.6% in each year before 1996 to 4.9% in 1997¹². It is possible that

HIV-infected individuals may survive longer because of the improved means of administering prophylaxis and treating the opportunistic infections, and so there is continued B-cell stimulation and the inevitable dysregulation, and all this has caused an increased incidence of lymphoma over time^{6,12}. Yet there is a recent publication from an international collaborative group that's studying 48,000 HIV-seropositive individuals from the United States and Europe; further, Australia reported a 42% decline in the incidence of NHL from 1997 through 1999, as compared with 1992 through 1996. Especially, there were significant decreases of plasmablastic and immunoblastic lymphoma, whereas the incidence of Burkitt's lymphoma was unchanged^{13,14}. The declining incidence following the introduction of HAART is reassuring because of there have been significant improvements that have boosted patients' immunity, as is highlighted by the increased CD4 cells counts.

In the early years of treating AIDS related lymphoma, a combination chemotherapy that consisted of high concentrations of cytosine arabinoside, methotrexate and cyclophosphamide was the recommended optimal therapy. However, the combination chemotherapy regimens that are commonly used for the treatment of intermediate or high grade lymphoma are so toxic that the occurrence of hematologic complications and opportunistic infection has generally resulted in a poor outcome for patients with AIDS related lymphoma. The AIDS Clinical Trial Group compared standard-dose therapy with methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethason (m-BACOD) along with granulocyte macrophage colony-stimulating factor (GM-CSF) with a reduced-dose m-BACOD with GM-CSF. The results of that study demonstrated that complete response was achieved by 52% of the patients with using standard-dose therapy and 41% of the patients achieved CR with using low-dose therapy; there were no significant differences in the response rates between standard dose and low-dose m-BACOD therapy. Only the hematologic toxicity was statistically significantly less for the dose modified regimen¹⁵. Recent study using 6 cycles of dose-adjusted EPOCH regimen showed 74% complete response rate. The addition of Rituximab to the CHOP regimen increased the complete response rate and prolonged survival without any increase in toxicity¹⁷. The same as for the case of primary central nervous system lymphoma (PCNSL), it's a common practice to use brain radiation and steroid therapy to alleviate symptoms.

Our first patient with PCNSL responded well to radiation therapy, but he finally died of pneumonia. He had history of long-term use of immunosuppressants including steroid, and he had undergone splenectomy for thrombocytopenia. The second case was treated with the CHOP regimen. He also had chronic B-type hepatitis at the time of presentation. The third patient achieved partial remission after receiving 6 cycles of the

R-CHOP regimen, and the fourth patient achieved complete remission after receiving 4 cycles of dose adjusted EPOCH regimen. Clearly, the response to chemotherapy and patient survival were related with existing comorbidities and the patients' general condition.

The CD4 count is considered to be one of the most important predictors of AIDS-related lymphoma patients. Tumor invasion other than to the lymph node, the performance status, the histologic subtype and the clinical stage could also be useful as predictors¹⁰. The adverse prognostic factors for AIDS related lymphoma include a CD4 count of $<100/\text{mm}^3$, a Karnofsky Performance Status score of $<70\%$, an age >35 years, stage III or IV disease, an elevated LDH level and a history of drug injection abuse. AIDS related lymphoma patients exhibit various degrees of immune suppression. At the time of diagnosing lymphoma, the CD4 counts of our patients were $46/\text{mm}^3$, $290/\text{mm}^3$, $420/\text{mm}^3$ and $317/\text{mm}^3$, respectively. The CD4/CD8 ratios were 0.07, 0.51, 0.36 and 0.1 respectively.

The 1 year survival rate of AIDS related lymphoma patients is 30%, which is lower than the general lymphoma population. The prognosis for both high-grade and low-grade lymphoma patients has been found to be rather poor².

When examining the trends of AIDS patients, the incidence of AIDS-related lymphoma is expected to increase. Yet the exact pathogenesis of HIV-related lymphoma has still not been determined. The development of new pharmaceuticals could help improve patients' immune systems, which would enhance the prognosis of AIDS related lymphoma, but HAART plays only a slight role for treating AIDS related lymphoma as compared to reducing the other opportunistic infections. The choice of regimen, the frequency of treatment and the dosage of the chemotherapeutic agents should be decided on by considering the prognostic difference on a case by case basis. Further clinical trials should be conducted to determine the most effective therapies.

SUMMARY

We have experienced four cases of lymphoma that developed in AIDS patients. All of the cases developed this while on HAART treatment. We highly recommend that any single mass lesion in an AIDS patient should be viewed as a possible lymphomatous lesion; this should be pathologically confirmed for early detection and proper management. We report here on our 4 Korean AIDS patients with lymphoma; they all had lymphoma at different anatomical sites and they presented with their own distinct clinical features at presentation.

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