Myelodysplasia Associated with Acquired Immunodeficiency Syndrome

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Abstract

Two cases of acquired immunodeficiency syndrome with myelodysplasia are presented. Case 1 was admitted because of *Pneumocystis carinii* pneumonia. Mild anemia, thrombocytopenia and hypersegmented neutrophils were observed. After the administration of trimethoprim-sulfamethoxazole and antiretroviral therapy, pancytopenia progressed. Bone marrow (BM) showed dysplastic hematopoiesis, suggesting human immunodeficiency virus-myelopathy. Case 2 was hospitalized due to progressive multifocal leukoencephalopathy. BM specimen obtained for thrombocytopenia showed myelodysplasia similar to myelodysplastic syndrome, suggesting that HIV may have an influence on hematopoietic progenitor cells.

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Key words: human immunodeficiency virus (HIV) infection, pancytopenia, myelodysplastic syndrome, HIV-myelopathy, hematopoietic progenitor cells

Introduction

Hematologic abnormalities are found in most patients with human immunodeficiency virus (HIV) infection (1, 2), particularly in later phases of the disease. Anemia, leukopenia, thrombocytopenia or pancytopenia are often observed. However, the causes of these abnormalities are usually multifactorial, and commonly can be attributed to hematopoietic suppression of bone marrow due to infection or drugs. Dysplastic hematopoiesis is also a common finding accompanying HIV infection (3, 4). If the well-defined criteria for the diagnosis of myelodysplastic syndrome (MDS) are applied, most hemopoietic findings in acquired immunodeficiency syndrome (AIDS) do not correspond to the significant maturation defects comparable with MDS. In a large number of cases, bone marrow (BM)

findings seem to be nonspecifically abnormal. Therefore, bone marrow lesions accompanying AIDS may be separated from MDS and diagnosed as HIV-myelopathy.

In this article we report two cases of AIDS with dysplastic hematopoiesis. HIV infection may induce HIV-myelopathy, or MDS results from the influence on hematopoietic progenitor cells (HPC), and MDS contributes to peripheral pancytopenia through ineffective hematopoiesis.

Case Report

Case 1

A 66-year-old man was admitted to our hospital on October 8, 1998, because of severe pneumonia. He had no past history except for hepatitis B.

On admission, laboratory data showed mild normochromic anemia (hemoglobin 12.0 g/dl) and thrombocytopenia (platelet count $9.6 \times 10^4/\mu\text{l}$). The white blood cell (WBC) count was $6,000/\mu\text{l}$, and the differential revealed 73% neutrophils and 16% lymphocytes. Hypersegmentation of the neutrophils was observed. The levels of lactic acid dehydrogenase (LDH) (1,249 IU), C-reactive protein (CRP) (18.2 mg/dl) and (1 $\rightarrow$ 3)- β -D-glucan (>300 pg/ml) were elevated. Analysis of arterial blood gas showed that the partial pressure of oxygen was 49.8 Torr, the partial pressure of carbon dioxide was 27.7 Torr, and pH was 7.465. Chest radiograph and chest computed tomography (CT) showed diffuse interstitial infiltrations. *Pneumocystis carinii* was detected from the bronchoalveolar lavage (BAL) fluid by Grocott staining and polymerase chain reaction (PCR). As HIV-1, 2 antibodies and Western blotting for HIV-1 antibody were both positive, he was diagnosed as having acquired immunodeficiency syndrome (AIDS) complicated with *Pneumocystis carinii* pneumonia (PCP). The CD4+ cell count was $37/\mu\text{l}$ and HIV-1-RNA viral load was 8.6×10^4 copies/ml. Trimethoprim and sulfamethoxazole (TMP-SMX) with glucocorticoid therapy was effective, and PCP was improved. After about 1 month, highly active antiretroviral therapy (HAART), that is, zidovudine, lamivudine and nelfinavir was started. As

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WBC count was decreased to 1,300/ μ l (neutrophils 9%) on November 9, granulocyte colony-stimulating factor (G-CSF) was administered. On November 12, he suffered from pneumonia again. Culture of BAL fluid yielded *Aspergillus flavus*. As the pneumonia was improved by the administration of amphotericin B, he was discharged on February 2, 1999 (Fig. 1).

As pancytopenia (WBC 2,700/ μ l, neutrophils 9%, hemoglobin 10.4 g/dl, MCV 114.2 fl, platelet 7.3×10^4 / μ l) developed, bone marrow (BM) was examined on February 22, 1999. Although BM cellularity was normal, morphologic abnormalities of giant stab, hypersegmentation and defective granulation of neutrophils, distorted nuclear and cytoplasmic maturation, multinucleation of erythroblasts were observed (Fig. 2). Chromosome analysis was 46, XY. The serum levels of vitamin B12 and folic acid were in the normal range.

Case 2

A 25-year-old man complained of fever on October 13, 1997 and one week later, language disturbance and difficulty with

handwriting appeared. He was admitted to our hospital on November 5. He had been diagnosed as having HIV infection, and zidovudine had been administered in another hospital in December 1994. When he came to our out-patient clinic in November 1996, CD4+ cell count was 39/ μ l and platelet count, 7.5×10^4 / μ l.

On admission, he did not show abnormal neurologic findings except for slight ataxia on the right upper extremities. His WBC count was 3,400/ μ l and the differential revealed 38% neutrophils and 44% lymphocytes. He showed thrombocytopenia (platelet count 6.1×10^4 / μ l) without anemia. CD4+ cell count was 91/ μ l, and HIV-1-RNA viral load was 5.5×10^4 copies/ml. The culture of cerebrospinal fluid (CSF) was negative. A T2-weighted magnetic resonance imaging (MRI) showed an increased high intensity signal in the white matter of bilateral frontal lobe. Didanosine and indinavir were started. At the end of November 1997, he showed hemiparesis on the right side. Platelet count was decreased to 4.5×10^4 / μ l. The level of platelet associated IgG (PAIgG) was 73.5 ng/ 10^7 cells (normal range

Figure 1. Clinical course of case 1. TMP-SMX: trimethoprim and sulfamethoxazole, FLCZ: fluconazole, AMPH-B: amphotericin B, PAPM: panipenem/betamiprom, MINO: minocycline hydrochloride, GCV: ganciclovir, G-CSF: granulocyte colony-stimulating factor, AZT: zidovudine, 3TC: lamivudine, NFV: nelfinavir, WBC: white blood cell, CRP: C reactive protein, CMV: Cytomegalovirus.

Figure 2. Morphologic abnormalities in bone marrow of case 1 (May-Giemsa stain, $\times 1,000$). A: Hypersegmentation of neutrophils, B: Hypogranulation of neutrophils, C, D: Multinucleation of erythroblasts.

9.0–25.0). CD4+ cell count was 112/ μ l and viral load was less than 400 copies/ml. The serum level of vitamin B12 was high and folic acid was in the normal range. JC virus was detected from the CSF by PCR. He was diagnosed as having progressive multifocal leukoencephalopathy. BM aspirates were obtained for the examination of thrombocytopenia. BM specimen demonstrated slightly hypercellular marrow and morphologic abnormalities of hypo- or hypersegmentation, reduced or absent granulation of neutrophils, distorted nuclear and cytoplasmic maturation, and multinucleation of erythroblasts (Fig. 3). Neutrophil alkaline phosphatase (NAP) score was diminished to 139 (control 405). Chromosome analysis was 46, XY. These findings were similar to MDS. Although CD4+ cell count was increased to 268/ μ l, his neural findings rapidly worsened and dysphagia appeared. After antiretroviral therapy was stopped, peripheral pancytopenia gradually progressed. WBC count was 1,300/ μ l (neutrophils 61, lymphocytes 29%), hemoglobin 5.1 g/dl and platelet count 2.3×10^4 / μ l in July 1998. BM

aspirates were obtained, and the findings were similar to the last one. He suffered from sepsis repeatedly (*Staphylococcus epidermidis*, *Candida albicans*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, *Enterococcus faecalis*, methicillin resistant *Staphylococcus aureus*) (Fig. 4).

Discussion

Pancytopenia is found in most patients with AIDS, particularly in the advanced phases. The mechanisms are commonly associated with the hematopoietic suppressive effects of HIV on HPC or marrow stromal cells, of certain types of infection (CMV, parvovirus, hepatitis virus and mycobacterial infection), or of drugs used in acquired immunodeficiency syndrome (AIDS)-related therapy (zidovudine, gancyclovir, TMP-SMX).

The most consistent HIV-related hematopoietic abnormality is the regenerative BM failure in which on-demand hematopoiesis is suppressed. There is clear evidence that HIV infec-

Figure 3. Morphologic abnormalities in bone marrow of case 2 (May-Giemsa stain, $\times 1,000$). A: Hyposegmentation of neutrophils, B: Hypersegmentation of neutrophils, C: Hypogranulation of neutrophils, D: Multinucleation of erythroblasts.

tion of auxiliary cells, mainly macrophages and microvascular endothelial cells (MVEC) (5) and viral gene products can indirectly influence survival and growth of HPC. The production of hematopoietic growth factors by HIV infected-auxiliary cells is normal, but lipopolysaccharide (LPS)-induced production of granulocyte-macrophage colony-stimulating factor (CSF), macrophage-CSF, G-CSF, interleukin (IL)-1 or IL-6 is significantly reduced (6). Moreover HIV inhibits replication of HPC by inducing release of multiple mitotic inhibitory factors (7, 8) and expression of factors known to induce apoptosis (9). These mechanisms can cause peripheral pancytopenia in association with BM failure. However, these studies have not suggested that HIV causes myelodysplasia or MDS.

On the other hand, myelodysplasia is also a common finding accompanying HIV infection. As dysplastic hematopoiesis in AIDS patients usually seems to be nonspecific change, it is called HIV-myelopathy. Cases of AIDS complicated with MDS seem to be rare (10, 11). As most patients with AIDS have

already received myelotoxic therapy prior to marrow examination, it is difficult to specify the cause of dysplastic hematopoiesis. In other words, it is possible that the dysplastic changes could be related to drugs or infections. Inoue et al showed that long-term exposure of zidovudine produces myelodysplasia in mice (12). It is generally assumed that DNA elongation is stopped by the insertion of zidovudine into the chain in place of thymidine and therefore possible to link to the qualitative abnormality of HPC. Gancyclovir and TMP-SMX have not been reported to cause myelodysplasia. Viral infections usually can cause cytopenias in association with BM suppression. There are a few reports which discuss myelodysplasia caused by viral infection. Baurmann et al reported that bone marrow infection by parvovirus B19 could closely mimic myelodysplasia (13).

We reported two cases of myelodysplasia associated with AIDS. In case 1, mild anemia, thrombocytopenia and hypersegmented neutrophils were observed before the admin-

Myelodysplasia and AIDS

Figure 4. Clinical course of case 2. AZT: zidovudine, DDI: didanosine, 3TC: lamivudine, IDV: indinavir sulfate ethanolate, TMP-SMX: trimethoprim and sulfamethoxazole, G-CSF: granulocyte colony-stimulating factor, WBC: white blood cell, Hb: hemoglobin, Plt: platelet, NCC: nucleated cells count, Mgc: megakaryocytes.

istration of TMP-SMX and antiretroviral therapy. The bone marrow findings of hypersegmented neutrophils and dysplastic erythroblasts suggested the abnormality of nucleic acid metabolism due to drugs, in addition to the inflammatory-reactive changes (HIV-myelopathy). The defects of nuclear lobulation of mature neutrophils and micromegakaryocytes which were features of MDS were not observed. In case 2, the BM specimen demonstrated slightly hypercellular marrow and

morphologic abnormalities of pseudo-Pelger-Huët anomaly, hypersegmentation, reduced or absent granulation of neutrophils, distorted nuclear and cytoplasmic maturation, multi-nucleation of erythroblasts. NAP score was diminished. Peripheral pancytopenia has gradually progressed after discontinuation of antiretroviral therapy. These findings were similar to MDS (Table 1). Table 1 shows the comparison of hematologic changes between HIV-myelopathy and MDS (except for

Table 1. Comparison of Hematologic Findings and Bone Marrow in Patients with HIV Infection and MDS (3, 4)

	HIV (n=40)	MDS (n=40)	Case 1	Case 2
Mean Hb (g/dl)	10.8	8.9*	10.4	5.1
Quality of anemia	normocytic	macrocytic	macrocytic	macrocytic
Mean WBC ($\times 10^3/\mu\text{l}$)	5.2	3*	2.7	1.3
Mean plts ($\times 10^3/\mu\text{l}$)	196	132	73	23
Bone marrow cellularity	$\rightarrow \sim \uparrow$	$\uparrow \sim \uparrow \uparrow *$	$\rightarrow$	$\uparrow$
Granulopoiesis				
increase of blasts	rare	+	—	—
shift to the left	+	+	+	—
giant bands	+	+	+	+
increase of monocyte-like cells	+	uncommon	—	—
hypogranulation	uncommon	+	+	+
hypersegmentation	uncommon	+	+	+
hyposegmentation	uncommon	+	—	+
Erythropoiesis				
shift to the left	+	+	+	+
macrocytic to megaloblastoid	not often	often*	+	+
defect in nuclear-cytoplasmic maturation	not often	often*	+	+
multinucleation	not often	often*	+	+
Megakaryopoiesis				
micromegakaryocytes	rare	+	—	—
atypical lobulation	uncommon	often*	—	—

*statistical significance $p \leq 0.05$. HIV: human immunodeficiency virus, MDS: myelodysplastic syndrome, Hb: hemoglobin, WBC: white blood cell, plts: platelets.

chronic myelomonocytic leukemia and refractory anemia with excess of blasts in transformation). In contrast to the inconspicuous changes of hemopoietic cells in AIDS, MDS showed a variety of morphologic abnormalities (3, 4).

Because MDS results from an abnormality of HPC, it is very important to focus on the direct influence of HIV on HPC (14). Current studies suggest that HIV infection of HPC is infrequent and not substantially involved in the pathogenesis of marrow failure. However, it has already been shown that a small fraction of enriched marrow progenitors express both CD34+ and either CD4+ or gp120+ (15). Recently, it was shown that CXCR4 transcripts were detected in CD34+ cells (16). We observed that pathogenic simian/human immunodeficiency virus (SHIV) induced dysplastic hematopoiesis which might result from the effect on HPC (Yoshino N et al, manuscript in preparation). Based on these facts, HPC may be infectable under certain conditions.

Although thrombocytopenia is not common as an isolated early manifestation of MDS, thrombocytopenia was present at the time of diagnosis of MDS in case 2. As his PAIgG level was high, he might be diagnosed as HIV-related thrombocytopenia without evaluation of bone marrow findings. There are recent reports that megakaryocytes express CXCR4 and CD4 (17). It becomes important to evaluate the role of direct infection of these cells by HIV. It is possible that some of the pa-

tients diagnosed as HIV-related thrombocytopenia may be MDS.

We suggest that HIV infection induces MDS which results from the direct influence on HPC and MDS contributes to peripheral pancytopenia through ineffective hematopoiesis. When peripheral blood cytopenia is observed in patients with AIDS, MDS should be included in the differential diagnosis.

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