Pure Red Cell Aplasia Induced by Lamivudine without the Influence of Zidovudine in a Patient Infected with Human Immunodeficiency Virus

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Abstract

We herein report the case of a patient with human immunodeficiency virus infection and acquired immune deficiency syndrome who was diagnosed with drug-induced pure red cell aplasia consequent to lamivudine treatment. The patient was admitted to our hospital for treatment of increasing shortness of breath following physical effort. Upon admission, routine blood tests revealed a hemoglobin level of 7.6 g/dL and a hematocrit proportion of 21.2%, with normal leukocyte and platelet counts. After stopping the lamivudine treatment, the patient’s hemoglobin concentration and hematocrit level returned to normal. A bone marrow examination showed an exclusive reduction in erythrocyte formation. This case indicates that lamivudine can induce severe anemia without the influence of zidovudine.

Key words: 3TC, ZDV, PRCA

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Introduction

Antiretroviral therapy (ART) regimens including the nucleoside reverse transcriptase inhibitor (NRTI) lamivudine (3TC) are considered first-line therapy for human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections according to the current treatment guidelines (1). Furthermore, 3TC is known to delay viral resistance to zidovudine (ZDV) and enhance the effects of ZDV in patients previously treated with ZDV (2). However, anemia has been reported in 3TC-treated patients who have received either concomitant or previous ZDV treatment (3-5). A case of 3TC-induced pure red cell aplasia (PRCA) was recently reported in an HIV-infected patient with an acute bacterial infection who had not been previously treated with ZDV (6). In this report, we describe a case of 3 TC-induced PRCA in a young HIV patient who received ART without a concurrent or previous history of ZDV treatment. In this case, PRCA manifested as severe normocytic anemia and resolved after the discontinuation of 3TC.

Case Report

A young Asian bisexual man who had been diagnosed with HIV/acquired immune deficiency syndrome (AIDS) and treated with antiretroviral therapy (3TC; efavirenz: EFV; and abacavir: ABC) was admitted to our hospital due to shortness of breath and heart palpitations following exertion. He had been diagnosed with HIV/AIDS three months earlier, at which time he had exhibited a continuous low-grade fever, oral candidiasis and systemic lymph node swelling. At the time of diagnosis, his blood viral load was 100,000 cop-
ies/mL and his CD4+ T cell count was 320 cells/μL. ART was initiated at a once-daily oral dose consisting of 3TC (300 mg), EFV (600 mg) and ABC (600 mg). This therapy was well tolerated, with the exception of light vertigo, which persisted for several weeks after the initiation of EFV. The patient’s medical history included two episodes of duodenal ulcer bleeding due to excessive alcohol consumption; however, we found no signs of intestinal ulcers. However, we found no signs of intestinal bleeding. His bone marrow specimen showed a marked and exclusive decrease in the erythrocyte formation system (Figure); however, there was no evidence of malignant infiltration, granulomas or giant pronormoblasts—a reported pathognomonic sign of parvovirus B19-associated red cell aplasia (7-9). We then suspected a diagnosis of drug-induced anemia and replaced 3TC with stavudine (d4T). Seven days later, the patient’s blood Hb concentration and Hct level recovered to 10.3 g/dL and 31.8%, respectively (Table). A second red blood cell transfusion was not required because the Hct and Hb levels did not decrease after 3TC discontinuation. The patient was discharged three weeks later, and we observed no recurrence of anemia during a one-year follow-up period in the outpatient clinic.

Discussion

Post-ART anemia has been reported to occur at a rate of

### Table. Hematologic Profile of the Patient. Normocytic Anemia with Normal White Cell and Platelet Counts was Observed throughout the Patient’s Clinical Course

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>White blood cell count (× 10⁹ cells/L) (4-8)*</th>
<th>Hb (g/dL) (13.5-17.6)*</th>
<th>Hct (%) (39.8-51.8)*</th>
<th>MCV (fL) (82.7-101.6)*</th>
<th>MCH (pg) (28.0-34.6)*</th>
<th>Platelets (× 1,000/micro L) (150-350)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART initiation</td>
<td>6.3</td>
<td>13</td>
<td>37.2</td>
<td>83</td>
<td>29</td>
<td>205</td>
</tr>
<tr>
<td>On admission (3 months after ART initiation)</td>
<td>5.3</td>
<td>7.6</td>
<td>21.2</td>
<td>84</td>
<td>29.9</td>
<td>313</td>
</tr>
<tr>
<td>5 days after termination of 3TC</td>
<td>4.2</td>
<td>10.2</td>
<td>30.8</td>
<td>88</td>
<td>29.2</td>
<td>310</td>
</tr>
<tr>
<td>1 month after termination of 3TC</td>
<td>5.8</td>
<td>13.3</td>
<td>39.2</td>
<td>95</td>
<td>32.3</td>
<td>194</td>
</tr>
</tbody>
</table>

*Values in parentheses are the normal value ranges.

Figure. Bone marrow histology on admission. A marked reduction in the erythrocyte formation system was observed. Erythroid cells in the bone marrow=12.6%; myelocyte/erythrocyte ratio=5.22 (normal range: 1.5-3.3).
short duration of use in this case.

PRCA has been reported to be associated with a variety of clinical disorders, and various autoimmune mechanisms have been described to induce red blood cell formation (13, 14). Primary PRCA has been suggested to occur in response to both humoral and cellular immunity (15). Some PRCA cases have been documented to be associated with CD4+ T cell activation and a high CD4/CD8 ratio, and the existence of erythropoiesis-inhibiting T cells in the bone marrow has also been reported (13-15). In the present case, the patient’s peripheral blood CD4+ and CD8+ T cell counts and CD4/CD8 ratio were within the normal limits. Furthermore, we detected neither T cell proliferation in the bone marrow nor an elevated blood CD4/CD8 ratio; however, other clinical cases of PRCA in HIV patients have been reported in the absence of obvious T cell activation (5, 16). These facts suggest that PRCA can occur in HIV patients, who are expected to exhibit impaired T cell-mediated immunity.

In conclusion, we herein reported a case of PRCA induced by 3TC administration. We therefore warn physicians to recognize this rare adverse effect of 3TC, regardless of the presence or absence of a history of ZDV treatment.

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

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References

9.6/100 person-years and within the first two years of initial treatment regimens (8, 9) comprising the commonly prescribed combination of 3TC and ZDV (10). Additionally, 13 HIV-infected patients have been reported to have developed severe anemia in association with antiretroviral therapies including 3TC and ZDV (3). Furthermore, a case of severe anemia has recently been documented during the administration of 3TC- and ZDV-containing therapy (6). In addition, a case of 3TC-induced PRCA without ZDV treatment has been reported (6). The patient in that case was a 29-year-old HIV-infected woman under treatment with 3TC, d4T and EFV. She was admitted to the hospital with signs of acute infection (fever and high levels of inflammatory markers) and pancytopenia with severe microcytic anemia. That patient was initially treated with antibiotics for possible urosepsis. After antibiotic treatment, the other blood cell counts returned to the normal ranges; however, the reduced red blood cell count persisted, and the authors switched the patient from 3TC to tenofovir (TDF). Shortly after 3TC discontinuation (one week), the patient’s Hb level markedly improved. In contrast with that observed in our case, marked hypocellularity had been noted in that case following a bone marrow examination performed on admission (6). The authors also documented the presence of patchy cellular areas, including granulopoiesis and adequate megakaryocytes, neither of which were detected in the present case. We speculate that the granulopoietic and megakaryocytic areas identified in the previous case were due to the patient’s concomitant infection, as we did not observe marked hypocellularity or granulopoietic/megakaryopoietic areas in the bone marrow specimen obtained from our patient, who lacked any signs of acute infection. Consistent with other reports, the CD4+ T cell count and HIV load did not appear to affect the development of anemia in our case. In addition, autoimmune hemolysis, which can be caused by immune dysregulation in AIDS patients, was not observed in our patient, as demonstrated by the negative direct Coombs test and lack of an elevated haptoglobin level. Moreover, no red blood cell fragments were detected in the initial blood smears. Therefore, we excluded hemolysis as a possible contributing factor to the patient’s anemia. Furthermore, the results of drug lymphocyte stimulation tests against 3TC were negative. These findings indicate that 3TC exclusively damaged the erythrocyte formation system, thus resulting in PRCA.

In the present case, we used d4T as a substitute for 3TC instead of other NRTI alternatives, such as TDF and ZDV. TDF has been reported to cause renal proximal tubular dysfunction and decrease the glomerular filtration rate (11). In a recent report, Japanese patients with a small body weight (<59 kg) were shown to have an increased risk of renal insufficiency (12). In our case, given the patient’s small body weight (47.2 kg), TDF may have induced drug-associated renal dysfunction. We did not select ZDV because it has been reported to induce anemia (3, 6, 10). In contrast to the risks associated with TDF and ZDV, we believed that d4T would not cause frequent serious side effects during the