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Lamivudine-Induced Pure Red Cell Aplasia

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The aim of this report is to describe five patients with lamivudine-induced pure red cell aplasia, an association not previously described. We describe patients with unresponsive anemia in whom a complete study including blood cell counts, reticulocyte counts, hemolysis tests, and bone marrow aspiration was performed. Pure red cell aplasia was considered when anemia was associated with normal leukocyte and platelet counts with a corrected reticulocyte count below 1% and less than 5% bone marrow erythroid progenitors in the absence of positive hemolysis tests. Complete remission was considered when bone marrow erythroid progenitors were at least 16%. Five male patients had pure red cell aplasia with a median age of 32 years (range 29 to 37 years). Before lamivudine, they had hemoglobin >11.8 g/dl without transfusion requirements. After receiving the drug, hemoglobin dropped to 5.2 g/dl (4.3 to 6.1 g/dl) with high transfusion requirements and mean bone marrow erythroid progenitors of 1.84% (0 to 4%). Withdrawal of lamivudine was attempted to confirm the diagnosis. Seven weeks after stopping lamivudine, hemoglobin rose up to 12.8 g/dl (11.3 to 13.8 g/dl) and bone marrow erythroid progenitors increased up to 25.6% (21 to 40%) without transfusion requirements. Lamivudine-induced pure red cell aplasia may be a cause of anemia unresponsive to conventional treatment in AIDS. Since lamivudine use in Mexico has been relatively short, we expect more cases to appear in the future. Am. J. Hematol. 65:189–191, 2000.

Key words: pure red cell aplasia; anemia; lamivudine; nucleoside analogues

INTRODUCTION

Anemia is almost a universal finding in AIDS. Most of the times, it is attributed to generalized bone marrow failure or to autoimmune hemolytic processes. However, several other causes of anemia have been reported in patients with AIDS. The two most frequent causes of anemia in AIDS patients are related to either the cytopathic effect of the HIV or the antiviral drugs employed in the treatment of these patients. Antiretroviral drugs induce anemia due mainly to their suppressive effect on bone marrow cell precursors, generating bone marrow failure. However, other causes may be responsible for the anemia of the patient taking antiretroviral drugs. One of such causes is pure red cell aplasia (PRCA), which selectively affects erythroid bone marrow cells, inducing a nonresponsive anemia with a broad spectrum of intensity. The relationship between erythropoietic failure and viral diseases was described in 1948. This clinical entity, today recognized as PRCA, is associated with thymoma [1], hemolytic states [2], autoimmune diseases [3], malignant diseases [4,5], and drugs [6]. Since we found our first two patients with AIDS-related PRCA in 1996 [7], a prospective search for this clinical condition in every patient with anemia and refractoriness to regular treatment was started. We noticed that some retroviral agents were able to induce moderate to severe anemia; however, a true antiretroviral-induced PRCA was never demonstrated. Surprisingly, after diagnosis of the first lamivudine-induced PRCA, several other patients were found and because no previous reports in the literature about the association lamivudine and PRCA have been published, we describe herein five patients with this erythropoietic abnormality.

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TABLE I. Characteristics of Five Patients With Lamivudine-Associated Pure Red Cell Aplasia (PRCA)*

	1			2			3			4			5		
Patient	Hb	CRC	BMEP	Hb	CRC	BMEP	Hb	CRC	BMEP	Hb	CRC	BMEP	Hb	CRC	BMEP
Before diagnosis	12.9	1.2		13.4	ND		12.0	ND		13.8	14		11.8	0.8	
At PRCA diagnosis	4.8	0.2	2.0	5.2	0	0	4.3	0	1.8	6.1	0.7	3.0	5.6	0.5	1.2
3 weeks after diagnosis	5.3	28.0	12.1	5.9	26.0	17.0	5.0	29.0	13.0	7.1	28.0	16.0	6.1	35.0	13.0
5 weeks after diagnosis	5.7	7.0	26.0	11.6	17.0	29.0	14.0	20.0	29.0	10.8	4.0	25.0	12.9	8.0	52.0
7 weeks after diagnosis	12.1	5.0	22.0	13.2	1.5	22.0	13.8	1.0	44.0	11.3	4.0	23.0	13.6	2.0	21.0

*Hb, hemoglobin (g/dl); CRC, corrected reticulocyte count (%); BMEP, bone marrow erythroid progenitors (%); ND, not done.

PATIENTS AND METHODS

Regular daily treatment of AIDS patients in our hospital includes zidovudine (250 mg BID), lamivudine (150 mg BID), and either saquinavir (600 mg TID) or indinavir (800 mg TID). Also, as a prophylactic treatment, they receive trimethoprim-sulfamethoxazole (800/160 mg QD), on a daily basis.

Since lamivudine was administered for the first time in our hospital, 110 patients have received this drug on a regular basis. During this period, thirty-one patients were found as having an unresponsive anemia to the common dietetic measures, treatment with hematinics, erythropoietin, and/or treatment of associated illnesses like infectious diseases, Kaposi's sarcoma, etc. A complete study of the patient including blood cell counts, reticulocyte counts, serum levels of indirect bilirubin and lactic dehydrogenase, Coomb's tests, and bone marrow aspiration was performed in every case. We considered a patient as having PRCA when unresponsive anemia was associated with normal leukocyte and platelet peripheral counts with a corrected reticulocyte count below 1% and with less than 5% erythroid progenitor cells in the bone marrow in the absence of positive hemolysis tests.

Once PRCA was diagnosed, withdrawal of the drug was attempted to confirm the diagnosis. Instead of lamivudine, didanosine was started (200 mg BID). After recovery of lamivudine-associated PRCA, all laboratory tests were repeated. To be considered in complete remission bone marrow erythroid cellularity must be at least 20%.

RESULTS

During a four-month period, five patients were diagnosed as having lamivudine-associated PRCA. These were five male patients with AIDS with a median age of 32 years (range 29 to 37 years). Before starting lamivudine, all of them had hemoglobin >11.8 g/dl without transfusion requirements. After receiving the drug for a median time of 12 weeks (10 to 42 weeks), hemoglobin dropped in the next three months to 5.2 g/dl (4.3 to 6.1 g/dl) with high transfusion requirements. After a 6-week evolution time (3 to 7 weeks), bone marrow aspiration was performed. Bone marrow cellularity and myeloid and megakaryocyte progenitors were normal; however, mean erythroid progenitors was 1.84% (0 to 4%) and a PRCA diagnosis was established. Giant bone marrow normoblasts, a pathognomonic sign of parvovirus B19-associated PRCA, were never identified in these patients [8]. We specifically searched for this finding since it has been demonstrated that parvovirus B19 infection is a frequent cause of anemia in AIDS patients.

Description of our first patient is important. PRCA was diagnosed after suffering a prolonged anemia requiring frequent transfusions of packed red blood cells. Prednisone (1 mg/kg/day) during 4 weeks was attempted based on our previous experience with this treatment. However, no response was obtained, and he persisted with high transfusion requirements. At this point, lamivudine had not yet been stopped. After a careful review of his clinical chart, we noticed that the last antiretroviral drug used had been lamivudine. When both prednisone and lamivudine were discontinued, hemoglobin and erythroid progenitors rose up in only 3 weeks to 12.1 g/dl and 28%, respectively, without transfusion requirements. Two months after the first case, a second case with similar evolution was found, and, on the basis of experience with the first patient, lamivudine was immediately suspended after PRCA diagnosis without simultaneous treatments.

In the five patients of this report, we observed that, after stopping lamivudine, Hb rose up to 12.8 g/dl (11.3 to 13.8 g/dl) by the end of the seventh week after diagnosis. On the other hand, the bone marrow showed an increase in erythroid progenitors from a mean of 1.64% (0 to 4%) up to 25.6% (21 to 40%) without transfusion requirements. General response, in terms of hemoglobin, corrected reticulocyte counts, and bone marrow erythroid progenitors, is shown in Table I. Today, almost 269 patients have received lamivudine in our department; our incidence of lamivudine-associated PRCA is as high as 1.9%.

DISCUSSION

PRCA is an uncommon disease. It is almost always associated with a recent viral disease, although multiple causes have been described: thymoma, hematologic ma-

lignancies, autoimmune diseases, drugs and chemicals, pregnancy, severe nutritional deficiencies, etc. [1]. There are only a few AIDS-associated PRCA cases reported [8–10]. The most accepted mechanisms for AIDS-associated PRCA are an autoimmune response as a consequence of the immune-dysregulated status of AIDS (immunity initially directed against infectious agents), and the myelosuppressive effect of the antiretroviral therapy.

PRCA diagnosis is made in an anemic patient in whom both bone marrow cellularity and megakaryocyte and leukocyte counts are normal but erythroid precursors are absent. The patients in this report fulfilled these criteria. We excluded every possible condition known to be associated with PRCA, including nutritional deficiencies and the use of medications other than lamivudine since these are the two conditions most frequently associated with PRCA in patients with AIDS. Furthermore, parvovirus-associated PRCA, a very frequent cause of anemia in patients with AIDS, was also ruled out [8]. Moreover, our cases did not have autoimmune hemolytic anemia, as supported by the normal results of the direct Coomb's test and other laboratory tests for hemolysis as well as the lack of response to prednisone.

At the time of PRCA diagnosis, all five patients of this report were receiving zidovudine–lamivudine, a combination previously reported in the literature to be associated with PRCA [11]. Furthermore, they also received other drugs known to be associated with anemia or PRCA. However, resolution of PRCA appeared soon after discontinuation of lamivudine alone as evaluated by means of Hb levels, reticulocyte counts, and erythroid bone marrow progenitors. Therefore, we consider that this erythroid disease was indeed secondary to lamivudine.

Treatment with lamivudine as a monotherapy in patients with AIDS and chronic hepatitis B infection has not shown anemia to be an important effect of this drug [12,13]. Furthermore, anemia has been recognized as a side effect of lamivudine only when administered with zidovudine [14]. As a particular effect of lamivudine alone, PRCA had never been previously reported. However, we believe that this phenomenon has been underdiagnosed. We have a hypothesis on the lack of previous reports regarding this association. Based on the fact that bone marrow failure is the most accepted mechanism to explain zidovudine–lamivudine-induced anemia, it is possible that physicians treating HIV patients assume that withdrawal of these drugs is enough for the patient to recover. Indeed, since most of the patients with lamivudine-associated or zidovudine–lamivudine-associated anemia have a faster recovery after stopping the drugs, a PRCA diagnosis is never made because there is no bone marrow aspiration. Therefore, we suggest that, in those cases with anemia without response either to conventional treatment or to withdrawal of a specific medication, bone marrow aspiration should be always considered in order to exclude PRCA as this is the only method to establish this diagnosis. We are sure that, in some cases, lamivudine-associated PRCA will be diagnosed after performing bone marrow studies.

Although to our knowledge this is the first report about lamivudine-associated PRCA, we believe that this may be a frequent cause of anemia unresponsive to conventional treatment in AIDS. In our patients, lamivudine-associated PRCA appeared after a relative short-time exposure to the drug. Considering that lamivudine has been only recently approved for clinical use in our country, we expect more AIDS patients suffering this secondary effect of this nucleoside analogue in the near future.

REFERENCES

1. Dessypris EN. The biology of pure red cell aplasia. Semin Hematol 1991;28:275–284.
2. Tohda S, Nara N, Tanikawa S, Imai Y, Murakami N, Aoki N. Pure red cell aplasia following autoimmune haemolytic anaemia. Acta Haematol 1992;87:98–102.
3. Meyer RJ, Hoffman R, Zanjani ED. Autoimmune hemolytic anemia and periodic pure red cell aplasia in systemic lupus erythematosus. Am J Med 1978;65:342–345.
4. Freedman MH. Pure red cell aplasia in childhood and adolescence: pathogenesis and approaches to diagnosis. Br J Haematol 1993;85: 246–253.
5. Mitchel ABS, Pinn G, Pegrum GD. Pure red cell aplasia and carcinoma. Blood 1971;37:594.
6. Gill MJ, Ratliff DA, Harding LK. Hypoglycemic coma, jaundice and pure RBC aplasia following chloropropamide therapy. Arch Intern Med 1980;140:714–715.
7. Majluf-Cruz A, Luna-Castaños G, Nieto-Cisneros L. AIDS-related pure red cell aplasia. Am J Hematol 1996;51:171.
8. Frickhofen N, Abkowitz JL, Safford M, et al. Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. Ann Intern Med 1990;113:926–933.
9. Griffin TC, Squires JE, Timmons CF, Buchanan GR. Chronic human parvovirus B19-induced erythroid hypoplasia as the initial manifestation of human immunodeficiency virus infection. J Pediatr 1991;118: 899–901.
10. de Mayolo JA, Temple JD. Pure red cell aplasia due to parvovirus B19 infection in a man with HIV infection. South Med J 1990;83:1480–1481.
11. Karras A, Rabian C, Zylberberg H, et al. Severe anoxic hepatic necrosis in an HIV-hepatitis C virus co-infected patient starting antiretroviral triple combination therapy. AIDS 1998;12:827–829.
12. Ingrand D, Weber J, Boucher CA, et al. Phase I/II study of 3TC (lamivudine) in HIV-positive, asymptomatic or mild AIDS-related complex patients: sustained reduction in viral markers. AIDS 1995;9: 1323–1329.
13. Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. A preliminary trial of lamivudine for chronic hepatitis B infection. N Engl J Med 1995;333:1657–1661.
14. Katlama C, Ingrand D, Loveday C, et al. Safety and efficacy of lamivudine–zidovudine combination therapy in antiretroviral-naive patients. A randomized controlled comparison with zidovudine therapy. JAMA 1996;276:118–125.