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Successful Treatment of Diamond-Blackfan Anemia With Metoclopramide

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Diamond-Blackfan anemia (DBA) is a congenital anemia characterized by a low reticulocyte count, the absence or severe reduction of hemoglobin-containing cells in the bone marrow, and normal megakaryocytic and granulocytic differentiation. Although the anemia may initially respond to corticosteroid therapy, many patients require lifelong red blood cell (RBC) transfusion, leading to infectious complications and iron overload. Metoclopramide has recently been used to treat DBA. Treatment with metoclopramide induces the release of prolactin from the pituitary and stimulates erythropoiesis. For these reasons, we used metoclopramide to treat a 20-year-old man with DBA refractory to low and high doses of corticosteroids, cyclosporin A, and tacrolimus (FK506). The hemoglobin and hematocrit slowly increased, and he has remained asymptomatic and transfusion-independent for 8 months. Metoclopramide therapy should be considered in patients with refractory DBA before treatment-related complications develop. Am. J. Hematol. 78:295–298, 2005. © 2005 Wiley-Liss, Inc.

Key words: Diamond-Blackfan anemia; metoclopramide; prolactin

INTRODUCTION

Diamond-Blackfan anemia (DBA) is characterized by severe anemia, reticulocytopenia, and decreased or absent bone marrow erythroid precursor cells and is frequently associated with such physical anomalies as short stature and craniofacial, cervical, and thenar malformations [1,2]. DBA is a heterogeneous disorder in which several pathophysiologic mechanisms may result in disturbed erythropoiesis at various stages along the erythroid differentiation pathway. The genetic basis of DBA is also likely heterogeneous. Abnormalities of the gene encoding ribosomal protein S19 (chromosome 19q13.2) have been reported in 25% of families, whereas linkage to different chromosomes have been implicated in other families [2]. Although the anemia may initially respond to corticosteroid therapy, many patients require lifelong red blood cell (RBC) transfusion, leading to infectious complications and iron overload. Other therapies include androgens, cyclosporin A, interleukin-3, high-dose methylprednisolone, antithymocyte globulin, and bone marrow transplantation [3–9]. Spontaneous remissions have been reported during adolescence [10,11].

Recently, metoclopramide has been shown to be an effective therapy for DBA [12]. Metoclopramide induces the pituitary release of prolactin [13,14], which improves erythropoiesis indirectly, perhaps mediated by bone marrow microenvironmental cells [12]. In this report, we describe the successful treatment with metoclopramide of refractory DBA in a 20-year-old man.

CASE REPORT

A 20-year-old Japanese man had been born at 40 weeks' gestation (birth weight, 2,655 g) via an uncomplicated vaginal delivery as the first child of

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non-consanguineous parents. He received a RBC transfusion at birth because of severe anemia (hemoglobin concentration, 5.0 g/dL). DBA was diagnosed at the age of 9 months old on the basis of bone marrow examination, which showed a hypoplastic erythropoiesis. Serological test results were negative for parvovirus and cytomegalovirus. Genetic analysis of ribosomal protein S19 was not performed. He received RBC transfusions 1 or 2 times per month. He underwent cataract surgery in July 1991 at the age of 7 years. His family history was remarkable, as his mother had pure red cell aplasia. He was treated with vitamin B_{12}, prednisolone, and methylprednisolone pulse therapy (30 mg/kg/day for 3 days) without improvement. Severe anemia necessitated RBC transfusions every 2 weeks, with subcutaneous injection of deferoxamine mesylate. Treatment with oral cyclosporin A was started in July 1998. The dosage was initially 300 mg/day (6.3 mg/kg/day) and was gradually increased to 600 mg/day (12.7 mg/kg/day) to achieve a trough level of 200 μg/mL. The reticulocyte count (> 3%) and hemoglobin concentration began to increase after 10 months of treatment, after which DBA remained in remission.

However, the patient was admitted to our hospital in June 1999 because of severe anemia (hemoglobin concentration < 5.0 g/dL). Bone marrow biopsy revealed hypocellularity ($95.0 \times 10^3/\mu L$) and decreased erythropoiesis (myeloid/erythroid [M/E] ratio of 18:1) with normal granulocytic and megakaryocytic differentiation and a normal karyotype. Blood transfusions were given 2 or 3 times per month to maintain the hematocrit > 25%. The immunosuppressive therapy was changed from cyclosporin A to tacrolimus (FK506) in August 1999. After treatment with FK506 began at a dosage of 0.14 mg/kg/day orally, the reticulocyte count gradually improved from 0.4% to 1.2%. However, the severe anemia continued to necessitate RBC transfusions every 2 weeks. Secondary diabetes mellitus was diagnosed in January 2001, and subcutaneous injection of insulin was started. Moreover, the complications of dilated cardiomyopathy and arrhythmia (paroxysmal supraventricular tachycardia) developed. The patient was admitted to the intensive care unit because of diabetes mellitus, heart failure (ejection fraction, 18%), and renal failure (serum blood urea nitrogen, 47 mg/dL, and creatinine, 1.0 mg/dL) in July 2003.

After these symptoms improved, metoclopramide was started at a dosage of 10 mg orally 2 times daily on September 28, 2003, and was increased to 15 mg orally 3 times daily on October 23, 2003. At the start of treatment, the hematocrit was 19.7%, the reticulocyte count was 0.3%, and the serum erythropoietin level was 5,490 mU/mL (normal range, 8–36 mU/mL). The white blood cell ($6.1 \times 10^3/\mu L$) and platelet ($172 \times 10^3/\mu L$) counts were normal. Bone marrow examination could not be performed before the start of metoclopramide therapy because of arrhythmia and heart failure. The patient's response to metoclopramide therapy is shown in Fig. 1. The hemoglobin concentration and hematocrit slowly increased from 6.9 to 12 g/dL and from 19.7% to 34.0%, respectively. More importantly, the reticulocyte count increased gradually from 0.1% to 6.1% by the fourth week of metoclopramide therapy, such that transfusions were no longer necessary. Bone marrow examination performed on the 60^{th} day of metoclopramide therapy revealed normocellularity ($143 \times 10^3/\mu L$) and increased erythropoiesis (M/E = 1.4:1) with normal granulocytic and megakaryocytic differentiation. The serum level of prolactin before treatment with metoclopramide was 5.1 ng/mL (normal range, 1.5–9.7 ng/mL). After the start of metoclopramide therapy, the serum level of prolactin had increased to 100 ng/mL in October 2003 and to 61.3 ng/mL in December 2003.

DISCUSSION

In 1938, Diamond and Blackfan described a congenital, red cell aplasia characterized by decreased or absent bone marrow erythroid precursor cells, severe anemia, and reticulocytopenia [1,2]. Diamond-Blackfan anemia (DBA) is a heterogeneous disorder in which several pathophysiologic mechanisms may result in disturbed erythropoiesis at various stages along the erythroid differentiation pathway [4]. Moreover, DBA is frequently associated with congenital abnormalities. Although most cases of DBA are sporadic, inheritance is observed in 10–20% of patients, with a dominant or, more rarely, recessive pattern. Although DBA is diagnosed in more than 90% of patients by the age of 1 year, it has also been diagnosed in adults, including elderly persons. More than 50% of patients with DBA respond to prednisolone therapy, and some remain in remission long after treatment has ended. However, approximately 30% of patients become dependent on blood transfusions or prednisolone, leading to hemochromatosis or other adverse effects. Prolonged use of prednisolone from the neonatal period increases the risk of life-threatening infections. Other therapies include high-dose methylprednisolone, cyclosporin A, bone marrow transplantation, recombinant interleukin-3, androgens, and antithymocyte globulin [3–9]. However, such complications as hypertension, renal dysfunction, infection, and secondary malignancies have been reported with cyclosporin A therapy [4].

Metoclopramide has successfully been used to treat DBA [12]. Metoclopramide is a dopamine receptor antagonist and serotonin receptor agonist widely used

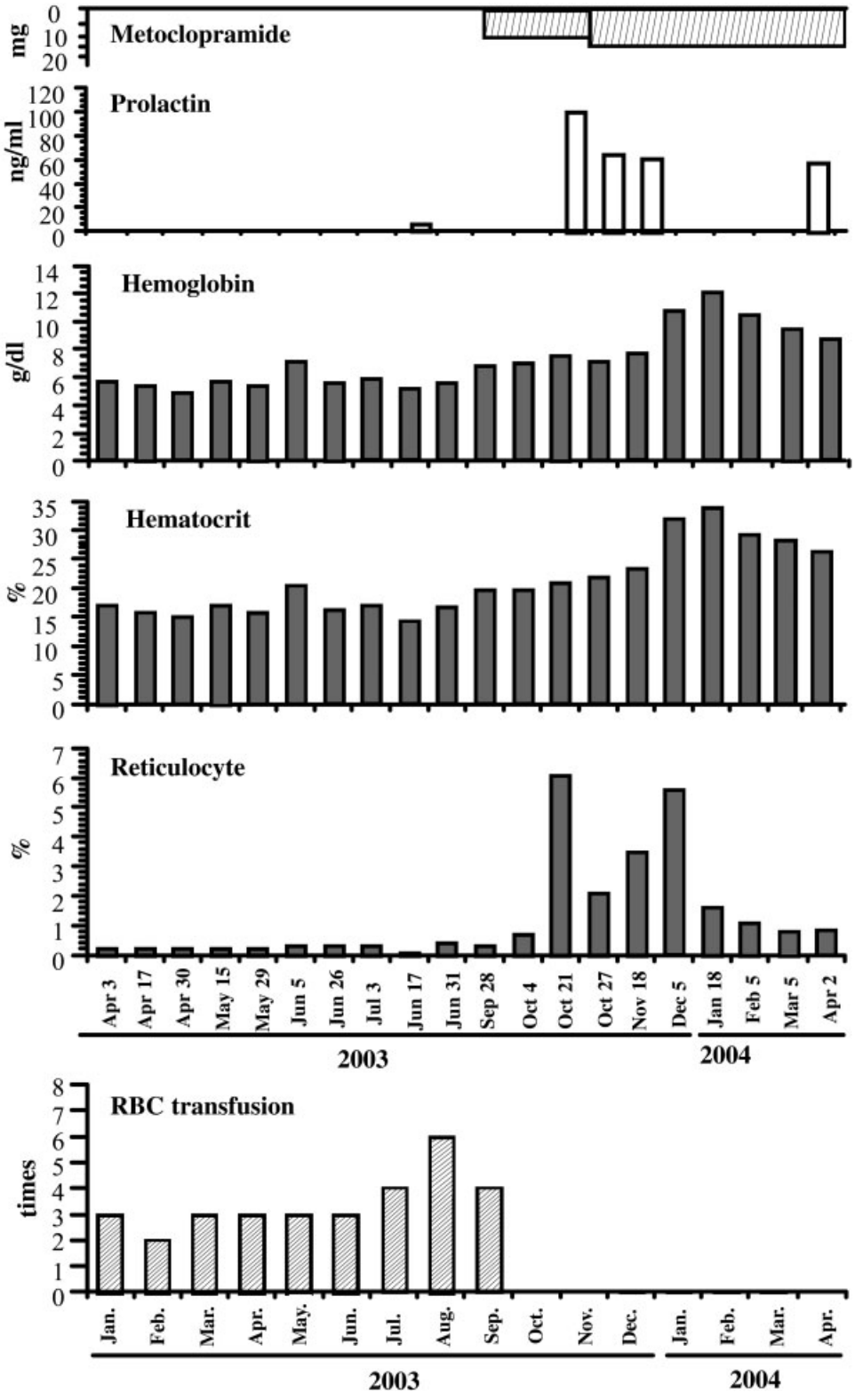

Fig. 1. Hematologic response of patient to metoclopramide. Metoclopramide was started at a dosage of 10 mg orally 2 times daily on September 28, 2003, and was increased to 15 mg orally 3 times daily on October 23, 2003. The serum level of prolactin increased from 5.1 to 100 ng/mL (October 27, 2003). The hemoglobin and hematocrit slowly increased from 6.9 to 12 g/dL and from 19.7% to 34.0%, respectively. The reticulocyte count increased gradually from 0.1% to 6.1% by the fourth week of metoclopramide therapy. RBC transfusion has not been required for 8 months since October 2003.

as an antiemetic and gastric prokinetic drug [15]. Moreover, metoclopramide induces prolactin release from the pituitary [13,14]. Case reports from the 1970s suggest that bovine prolactin, administered intramuscularly (600–900 μg/kg/day) may improve anemia [16]. Moreover, prolactin has been implicated in the support of erythropoiesis in vitro and in vivo [17]. Interestingly, our patient's mother had had pure red cell aplasia, and her anemia transiently improved during pregnancy. This transient improvement might be associated with increased prolactin secretion during pregnancy. The anemia responded to cyclosporin A, and continues to be in remission (last RBC transfusion, November 1999).

For these reasons, we used metoclopramide to treat a 20-year-old man with refractory DBA diagnosed at the age of 9 months old. He was treated with vitamin B_{12}, prednisolone, methylprednisolone pulse therapy, cyclosporin A, and FK506. Unlike his mother, he showed a transient improvement in reticulocyte count but required blood transfusions every 2 weeks because of severe anemia. Subcutaneous injection of deferoxamine mesilate is required, as chronic blood transfusion induces hemochromatosis due to iron overload (ferritin, 1,919 ng/mL [normal range, 40–350 ng/mL]). In addition, the patient has diabetes mellitus, arrhythmia, and severe heart failure. Metoclopramide was started at a dosage of 10 mg orally 2 times daily and was later increased to 15 mg orally 3 times daily. Metoclopramide induced prolactin secretion, such that the serum level of prolactin ranged from 61.3 to 100 ng/mL. The hemoglobin concentration and the hematocrit slowly increased from 6.0 to 12.0 g/dL and from 19.3% to 34.0%, respectively. More importantly, the reticulocyte count increased gradually from 0.1% to 6.1% after 4 weeks of metoclopramide therapy. The patient has remained asymptomatic and transfusion independent for 8 months.

Abkowitz et al. used metoclopramide to treat 15 patients with DBA; of the 9 patients who completed the planned 16 weeks of therapy, 3 responded [12]. Analysis of these results suggests that high serum concentrations of ferritin ($>4{,}000$ ng/mL), pituitary dysfunction, sex, and age may have contributed to the poor response to metoclopramide. Our patient responded, as shown by a serum ferritin concentration of 1,919 ng/mL and no clinical evidence of pituitary dysfunction.

The mechanism by which prolactin affects erythropoiesis is unclear. In vitro experiments have shown that exogenous prolactin does not increase burst-forming unit erythroid differentiation [12] and that prolactin receptors are not present on erythroid progenitor cells [12]. These results suggest that the action of prolactin on erythroid differentiation is indirect, possibly mediated by bone marrow environmental cells.

Metoclopramide is available for every patient, is inexpensive, and causes no life-threatening complications. Organized prospective trials of metoclopramide therapy should be performed in patients with DBA refractory to steroid and immunosuppressive therapies.

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