Pure Red Cell Aplasia and Diphenylhydantoin

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ABSTRACT

A patient was presented who developed pure red cell aplasia while taking diphenylhydantoin (300 mg/day) over a five-year period for the treatment of epilepsy. After discontinuation of diphenylhydantoin, the bone marrow showed a recovery from an erythroid aplasia and an intense reticulocytosis was observed in the peripheral blood. In spite of re-administration of diphenylhydantoin, anemia did not recur. The relationship between diphenylhydantoin and pure red cell aplasia was discussed.

Key words: pure red cell aplasia; diphenylhydantoin

INTRODUCTION

Pure red cell aplasia (PRCA) is an uncommon disorder characterized by severe anemia, absence of reticulocytes in the peripheral blood, and isolated depression of erythroid elements with normal production of granulocytes and platelets in the bone marrow. The disease occurs in two forms, the congenital and the acquired ones. A common incidence of congenital form has suggested an autosomal recessive mode of inheritance, but in some cases the disease appears to have been transmitted as an autosomal dominant trait. The congenital PRCA is occasionally associated with congenital abnormalities including a short stature and a retardation of bone age[1]. The acquired form is frequently noted with benign thymoma and represents a chronic state of reduced erythropoiesis[2]. In addition to the chronic state, acute aplastic crisis can occur during the course of infections, particularly viral infection, and also can be initiated by such drugs as chloramphenicol and chlorpropamide[3].

So far as we reviewed the recent literature, PRCA induced by

diphenylhydantoin (DPH) seems to be quite rare[4-6]. This paper reports a patient who developed PRCA while taking DPH for the treatment of epilepsy.

CASE REPORT

A 27-year-old woman was admitted to the Yamaguchi University Hospital on June 30, 1977, for an evaluation of anemia and its treatment. She began to have fever and cough two months before admission. The patient had been treated by a practitioner for acute bronchitis. Since then weakness, lethargy and pallor developed. The patient was given a transfusion of 400 ml of whole blood daily for five days. Laboratory examination at that time revealed a hemoglobin of 4.3 g/dl, a hematocrit of 15.5% and a white blood cell count of 3,700/mm^3. The patient was referred to the Yamaguchi University Hospital for further evaluation of anemia. She was known to have epileptic seizures from the age of 22 and was given every day 9 tablets of Hydantol F, 2 tablets of Tegretol and a half tablet of Trinuride, which contain 300 mg DPH, 100 mg phenobarbital and 400 mg carbamazepine. All three drugs were administered continuously until the time of admission.

Her past history was otherwise unremarkable. Her family history revealed that her father, paternal uncle and her aunt had epileptic convulsions.

On admission the patient was pale, her pulse was 84/min, respiration 20/min and blood pressure 110/60 mm Hg. There were no pertinent findings on physical examination.

Hematological findings on admission included the followings: red blood cell count, 307×10^4/mm^3; hemoglobin, 9.3 g/dl; hematocrit, 27.5 %; reticulocytes, 0.0%; platelets, 11.2×10^4/mm^3; white blood cell count, 2,800/mm^3, with 69% segmented forms, 5% band forms, 13% lymphocytes, 5% monocytes, 4% eosinophils, and 4% basophils. The erythrocyte sedimentation rate was 50 mm/h. A bone marrow aspirate showed complete absence of nucleated red blood cells. Serum iron was 192 μg/dl with a total iron binding capacity of 198 μg/dl. An examination of hemolytic and bleeding tendencies revealed no abnormalities. Chemical analysis of the blood showed an albumin and globulin ratio of 1.3, urea nitrogen 13 mg/dl, fasting blood sugar 90 mg/dl, and cholesterol 96 mg/dl. A serological examination revealed no abnormalities except for CRP +1. The serum electrolytes, an electrocardiogram and a urinalysis were all within normal limits. Roentgenography of the chest and pneumo-

mediastinography were normal and showed no evidence of thymic enlargement. Results of the bone marrow examinations are summerized in Table I. The changes of the reticulocyte number and the hemoglobin value during the hospitalization are illustrated in Figure 1.

A diagnosis of PRCA was made and prednisolone, 40 mg/day, was administered for four days. Administration of Hydantol and Trinuride was discontinued. During the following ten days, the number of reticulocytes reached a maximum of 22.8% and the hemoglobin value gradually increased (Fig. 1). The bone marrow examination at that time revealed marked erythroid hyperplasia (Table I). When the hemoglobin value reached the level of 10.0 g/dl, the patient was again given DPH 300 mg/day. During two weeks of observation there was no significant decrease in the reticulocyte count and hemoglobin value. The erythropoiesis in the bone marrow was restored to the normal range. The platelet count by the direct method and the total white blood cell count throghout the hospital course varied between 11.5 and $18.6\times10^4/mm^3$, and 1,900 and $7,400/mm^3$, respectively.

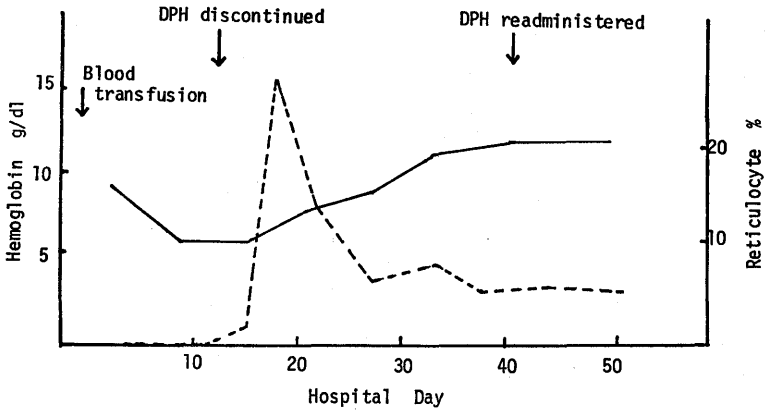

Fig. 1 Changes of hemoglobin value and reticulocyte count in peripheral blood. Solid line and dashed line are hemoglobin value and reticulocyte count, respectively.

DISCUSSION

The acquired form of PRCA is commonly associated with infection, malnutrition or thymoma. About a half of patients with acqired PRCA have thymoma[3], while about 5% of patients with thymoma develop PRCA[7]. Occasional cases, as in this case, are induced chemical drugs. The

Table I Bone Marrow Differential Counts (%)

	Hospital Day		
	1	22	44
Myeloblast	0.5		
Progranulocyte	3.3	0.3	1.5
Myelocyte	12.3	7.0	8.0
Metamyelocyte	18.8	6.8	11.3
N. Band	17.0	14.0	15.3
N. Segmented	22.0	9.3	17.8
Eosinophil	3.3	2.8	2.0
Basophil	0.3	0.0	1.0
Lymphocyte	18.1	5.0	21.7
Plasmocyte	0.5	0.5	0.5
Histiocyte	1.3	0.8	0.0
Monocyte	2.0	1.8	1.8
Rubriblast	0.0	0.5	0.0
Prorubricyte	0.0	0.5	0.3
Rubricyte	0.0	24.5	5.0
Metarubricyte	0.0	26.5	13.3
WBC:Nucleated RBC		0.9:1	4.4:1

Table II Hematological data of peripheral blood

	Hospital Day		
	8	18	38
RBC ($\times 10^4/mm^3$)	216	237	344
Ht(%)	19.6	22.7	33.0
Hb(g/dl)	6.6	7.4	11.1
Reticulocytes (%)	0.0	22.8	5.6
Platelets ($\times 10^4/mm^3$)	12.7	17.9	
WBC ($/mm^3$)	2,600	3,800	3,200

onset of acquired PRCA can be classified in two forms, acute aplastic crisis and chronic form. Our case with DPH-induced PRCA as well as previous reports[4-6] occurred in acute crisis.

Our case displayed slight leukopenia and thrombocytopenia. About 15% of the acquired PRCA patients have leukopenia and/or thrombocytopenia, but even in such cases the marrow reveals normal leukopoiesis and megakaryopoiesis[8].

Reduced erythropoiesis in PRCA may result from the supression of erythroblast development and/or from damage of the erythblasts formed. As for the etiology of reduced erythropoiesis in PRCA, an immune mechanism was suggested by Krantz and his colleagues[9,10], while Yunis et al[11] demonstrated that DPH exerts its toxic effect on hematopoiesis in DPH-induced PRCA by inhibiting DNA synthesis in erythroid precursors. Yunis et al recommended the administration of riboflavin to induce resistance to the toxic effect of DPH. Our case was malnourished after a respiratory infection when the anemia developed. The malnutrition improved after admission. The fact that anemia did not recur in spite of the re-administration of DPH suggests that the patient developed resistance to the toxicity of DPH to hematopoiesis. Lines of evidence indicate that riboflavin deficiency is associated with acquired PRCA[12-14]. Whether riboflavin had anything to do with this resistance remains to be clarified.

The most frequent hematological complication of DPH treatment is megaloblastic anemia[15]. According to Flexner and Hartman[16], the incidence of megaloblastic anemia is 0.75% in a large series of patients taking DPH.

In our case, carbamazepine (Tegretol), 400 mg/day, was administered along with DPH. Reversible PRCA can be induced by carbamazepine [17]. The anemia improved by the discontinuation of DPH alone. This led us to believe that DPH was the agent responsible. Whether a preceding respiratory infection and resulting malnutritional condition had some etiological significance in the development of PRCA or not remains unknown.

REFERENCES

1) Lawton, J.W.M., Aldrich, J.E. and Turner, Y.L.: Congenital erythroid hypoplastic anemia. Autosomal dominant transmisson. *Scand. J. Haematol.*, 13 : 276-280, 1974.
2) Krantz, S.B. and Zaentz, S.D.: Pure red cell aplasia. *The Year in Hematology*, Plenum Med. Book Co., New York, 1977, pp. 153-190.
3) Erslev, A.J.: Pure red cell aplasia. In: W.J. Williams, E. Beutler, A.J. Erslev and R.W. Rundles (eds). *Hematology*, McGrawhill Book Co. Inc., New York, 1977, pp. 278-287.
4) Brittingham, T.G., Lutcher, C.L. and Murphy, D.L.: Reversible erythroid aplasia induced by diphenylhydantoin. *Arch. Int. Med.*, 113 : 746-768, 1964.
5) Jeong, Y., Jung, Y. and River, G.L.: Pure RBC aplasia and diphenylhydantoin. *JAMA*, 229 : 314-315, 1974.
6) Ohno Y., Sato, M., Kurokawa, I., Moriyama, Y., Kinoshita, Y., Saito, H. and Terada, I.: Drug-induced erythroid aplasia (in Japanese). *Jpn. J. Clin. Hematol.*, 17 : 51-58, 1976.
7) Hirst, F. and Robertson, T.I.: The syndrome of thymoma and erythroblastopenic anemia. *Medicine*, 46 : 225-264, 1967.

8) Krantz, S.B.: Pure red cell aplasia. *Brit. J. Haematol.*, 25 : 1-6, 1973.
9) Krantz, S.B. and Kao, V.: Studies on red cell aplasia. I. Demonstration of a plasma inhibitor to heme synthesis an antibody to erythroblast nuclei. *Proc. Natl. Acad. Sci. USA*, 58 : 493-500, 1967.
10) Krantz, S.B., Moore, W.H. and Zaentz, S.D.: Studies on red cell aplasia. V. Presence of erythroblast cytotoxicity in IgG-globulin fraction of plasma. *J. Clin. Invest.*, 52 : 324-336, 1973.
11) Yunis, A.A., Arimura, G.K., Lutcher, CL, Balasquez, J. and Halloran, M.: Biochemical lesion in Dilantin-induced erythroid aplasia. *Blood*, 30 : 587-600, 1967.
12) Foy, H., Kondi, A. and Macdougall, L.: Pure red cell aplasia in marasmus and kwashiorkor - Treated with riboflavin. *Brit. Med. J.*, 1 : 937-941, 1961.
13) Lane, M. and Alfley, C.P.: The anemia of human riboflavin deficiency. *Blood*, 25 : 432-442, 965.
14) Foy, H., Kondi, A. and Verjee, Z.H.M.: Relation of riboflavin deficiency to corticosteroid metabolism and cell hypoplasia in baboons. *J. Nutrition*, 102 : 571-582, 1971.
15) Sparberg, M.: Diagnostically confusing complications of diphenylhydantoin therapy. *Ann. Intern. Med.*, 59 : 914-930, 1963.
16) Flexner, J.M. and Hartman, R.C.: Megaloblastic anemia associated with anticonvulsant drugs. *Am. J. Med.*, 28 : 386-396, 1960.
17) Hirai, H.: Two cases of erythroid hypoplasia caused by carbamazepine (Tegretol) (in Japanese). *Jpn. J. Clin. Hematol.*, 18 : 33-38, 1977.