Erythrocytosis in Hypophosphatemic Rickets: Irreversible Complication Due to Nephrocalcinosis after Vitamin D and Phosphate Therapy

Ryo OKAZAKI, Toshio MATSUMOTO, Shun-ichi HARADA, Seiji FUKOMOTO,
Toru MOTOKURA and Etsuro OGATA

A patient with hypophosphatemic vitamin D-resistant rickets developed secondary erythrocytosis during treatment with large doses of vitamin D₂ and phosphate. Erythrocytosis was accompanied by a fall in circulating plasma volume and appeared to have developed as a consequence of nephrocalcinosis because it occurred after the appearance of nephrocalcinosis following several episodes of hypercalcemia and hyperphosphatemia. Nephrocalcinosis and erythrocytosis did not disappear even after recovery of renal function. Thus, the present observations point to the importance of preventing these irreversible complications that could cause renal failure, erythrocytosis, and thrombotic events during the management of hypophosphatemic vitamin D-resistant rickets.

Key words: Hypophosphatemic rickets, Erythrocytosis, Nephrocalcinosis

Patients with hypophosphatemic vitamin D-resistant rickets (HVDRR) are usually treated with large doses of active vitamin D₃ or vitamin D₂ and phosphate. However, vitamin D therapy may sometimes cause hypercalcemia. If hypercalcemia develops under phosphate supplements, the combination therapy may cause irreversible dystrophic calcification such as nephrocalcinosis (1). Feest et al (2) reported that erythrocytosis was observed in 9 out of 250 patients with nephrocalcinosis. Because erythrocytosis associated with nephrocalcinosis is not accompanied by the increase in circulating plasma volume, these patients appear to be at high risk for thrombotic accidents. In this report, a HVDRR patient who exhibited nephrocalcinosis and erythrocytosis is presented. These abnormalities developed after episodes of hypercalcemia and hyperphosphatemia during the treatment with large doses of

vitamin D₂ and neutral phosphate. The importance of the prevention of hypercalcemia is discussed in order to avoid the irreversible complications of nephrocalcinosis and erythrocytosis.

CASE REPORT

A 23-year-old man with HVDRR was admitted to our hospital for the evaluation of erythrocytosis. At 2 yr of age, he was diagnosed as HVDRR, and the administration of large doses of vitamin D₂ (up to 320,000 U/day) was initiated. When he was 9 yr old, the first episode of hypercalcemia developed, and he was referred to another hospital where the diagnosis of vitamin D₂ intoxication was made. After discontinuation of vitamin D₂, his serum calcium level and renal function normalized. Smaller doses of vitamin D₂ were reinstituted combined with neutral phosphate. At 18 yr of age, hyperten-

From The Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Tokyo

Received for publication August 17, 1990; Accepted for publication January 30, 1991

Reprint requests should be addressed to Toshio Matsumoto, MD, The Fourth Department of Internal Medicine, University of Tokyo School of Medicine, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo 112, Japan

The present study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, and Grants for Abnormalities in Hormone Receptor Mechanisms from the Ministry of Health and Welfare of Japan

sion was noticed and hydrochlorothiazide was started. Morning plasma renin activity at recumbent position was low (0.03 ng/(l·s); normal range 0.22–1.22) and plasma aldosterone concentration was normal (220 pmol/l; normal range 60–360) before treatment. His hemoglobin level was normal before the administration of hydrochlorothiazide (around 140 g/l). Shortly after the addition of hydrochlorothiazide, serum calcium and phosphate levels began to rise followed by an increase in serum creatinine level. After the development of hypercalcemia (3.3 mmol/l; normal range 2.15–2.55 mmol/l) and hyperphosphatemia (2.2 mmol/l; normal range 0.8–1.4 mmol/l) with renal insufficiency (creatinine clearance 32 ml/min), the above therapy was discontinued. Although serum calcium, phosphate and creatinine levels all became normal, an elevation in red cell number and hemoglobin level (around 180 g/l) were noted. His hemoglobin level remained elevated thereafter, and he was referred to our hospital.

Physical examination was normal except for mild bowing of lower extremities and marginally elevated blood pressure (142/92 mmHg). The red blood cell count was $5.6 \times 10^6/\text{mm}^3$, hemoglobin 187 g/l and the hematocrit was 55%. Other blood cell counts were normal. Serum chemistry revealed that albumin was 48 g/l, calcium 2.3 mmol/l, phosphate 0.46 mmol/l and creatinine 110 $\mu\text{mol/l}$. As shown in Table 1, his parathyroid function was elevated, but

serum levels of vitamin D metabolites were within normal range except for the mild elevation in 25-hydroxyvitamin D. Although the red blood cell mass was markedly elevated, the total plasma volume was reduced. Plasma erythropoietin level was mildly elevated. The arterial blood oxygen saturation was normal. Computed tomography revealed focal areas of increased density in the medulla of bilateral kidneys.

DISCUSSION

Nephrocalcinosis during the course of HVDRR had been thought to be a rare complication of combined therapy with vitamin D and neutral phosphate. However, with the aid of new imaging devices such as ultrasonography and computed tomography, nephrocalcinosis has become one of the common complications of HVDRR. Goodyer et al (1) reported that nephrocalcinosis was found in 11 out of 23 HVDRR patients (48%) by ultrasonography. More sensitive devices such as computed tomography would reveal even higher incidence. Neutral phosphate therapy is known to cause complications such as secondary and tertiary hyperparathyroidism in patients with HVDRR (3). The high incidence of nephrocalcinosis further points to the importance of careful monitoring of serum calcium and phosphate levels during the course of such treatment.

Erythrocytosis with elevated serum level of erythropoietin, i.e. secondary erythrocytosis, develops mainly in association with hypoxemia and various renal diseases. Because the arterial oxygen saturation was normal in the present patient, erythrocytosis appeared to be caused by nephrocalcinosis. Although nephrocalcinosis is not a common cause of erythrocytosis, about 3.6% of patients with nephrocalcinosis are reported to exhibit erythrocytosis (2). In addition, because nephrocalcinosis mainly affects renal medulla, many of these patients exhibit disturbances in urine concentrating mechanisms. Thus, patients with nephrocalcinosis develop erythrocytosis without the concomitant increase in circulating plasma volume (2). Such features could be seen in the present patient. The combination of erythrocytosis with decreased plasma volume would certainly raise the risk of thrombotic accidents because of the increased blood viscosity.

Table 1. Laboratory Findings on Admission

	Patient	Normal
Endocrinological tests		
PTH-M, pmol/l	178	18.9–58.9
NcAMP, nmol/l glomerular filtrate	73	8–28
25-Hydroxyvitamin D, nmol/l	90.8	20–70
24,25-Dihydroxyvitamin D, nmol/l	1.7	1.0–4.8
1,25-Dihydroxyvitamin D, pmol/l	20.0	43–120
Hematological tests		
Circulating plasma volume, ml/kg	33.4	39–49
Red blood cell mass, ml/kg	53.4	33–39
Erythropoietin, U/l	26.5	9.7–25.9
Hemoglobin A ₂ , %	3.3	2.0–3.3
Hemoglobin F, %	<0.5	0–1.1

PTH-M, radioimmunoassay using antibodies against mid-portion of parathyroid hormone; NcAMP, nephrogenous cAMP

Although deterioration in some parameters of renal function during vitamin D and phosphate therapy of HVDRR is reversible, nephrocalcinosis and erythrocytosis do not disappear once they develop. Therefore, the present observations emphasize the importance of preventing these irreversible complications that could cause a variety of further problems including chronic renal failure and thrombotic episodes in the management of patients with HVDRR.

REFERENCES

- 1) Goodyer PR, Kronick JB, Jequier S, Reade TM, Scriver CR. Nephrocalcinosis and its relationship to treatment of hereditary rickets. *J Pediatr* **111**: 700, 1987.
- 2) Feest TG, Proctor S, Brown R, et al. Nephrocalcinosis: another cause of renal erythrocytosis. *Br Med J* **2**: 605, 1978.
- 3) Firth RG, Grant CS, Riggs BL. Development of hypercalcemic hyperparathyroidism after long-term phosphate supplementation in hypophosphatemic osteomalacia. *Am J Med* **78**: 669, 1985.