CASE REPORTS

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Antacid Induction of Phosphate Depletion Syndrome in Renal Failure

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DESPITE THE TENDENCY toward phosphate retention in chronic renal insufficiency, it has been shown that a state of phosphate depletion with its concomitant clinical sequelae can be produced in uremic patients by the use of phosphate binding antacids.[1-3] Moreover, symptoms of the phosphorus depletion syndrome—weakness, bone pain, malaise and mental depression—appeared to be reversible by phosphate repletion.[2,3] Osteomalacia or rickets or both have been described in patients who have phosphorus deficiency from either a renal loss or gastrointestinal losses.[4,5] Bone changes, however, have not been documented from phosphate depletion in uremia.

The promotion of gastrointestinal loss of phosphorus by aluminum hydroxide has led to its use as an acceptable therapeutic agent in patients who have hyperphosphatemia; and, in fact, it is widely employed in uremic patients as a means of controlling hyperphosphatemia.[6] Osteomalacia and osteitis fibrosa are both commonly identified in histologic sections of bone from these patients.[7,8] It is believed that osteomalacia is more common when dietary calcium is low and that low serum calcium and phosphorus ion product predisposes the bone to its development.[9] In the present study, phosphorus depletion and osteomalacia with bone fractures developed in a patient on chronic hemodialysis who was receiving aluminum hydroxide therapy.

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Report of a Case

The patient, a 42-year-old Mexican-American woman, was admitted to the Los Angeles County-University of Southern California Medical Center in June 1970 with complaint of fatigability and dyspnea. The illness which had progressed slowly during the preceding six months was characterized by increasing fatigue, weight loss, and loss of strength.

During the preceding four years the patient had had periodic attacks of arthritis involving the knees, wrists, ankles and great toe. She had taken colchicine with good relief, and had been told by her physician that she had gout. Except for periodic, temporary disability from her arthritic condition, she had been well until just before the onset of the present illness.

On examination at the time of admission the patient was observed to be short and mildly obese. She was sitting upright in bed, breathing rapidly and perspiring. Blood pressure was 108/90 mm of mercury, pulse 120, respirations 24, temperature 37°C (98.6°F). On funduscopic examination slight arteriolar narrowing was noted, but no hemorrhages or exudates. The neck veins were distended to the angle of the jaw with the patient in the sitting position, and the heart had a pronounced gallop rhythm. There were moist inspiratory rales heard on both sides of the chest. The liver was palpable 1 to 2 cm below the right costal margin. Moderate pretibial and ankle edema was noted. Gouty tophi were not seen. The knees and ankles showed some hypertrophy, though there was no limitation of motion.

Hemoglobin content was 8.8 grams per 100 ml

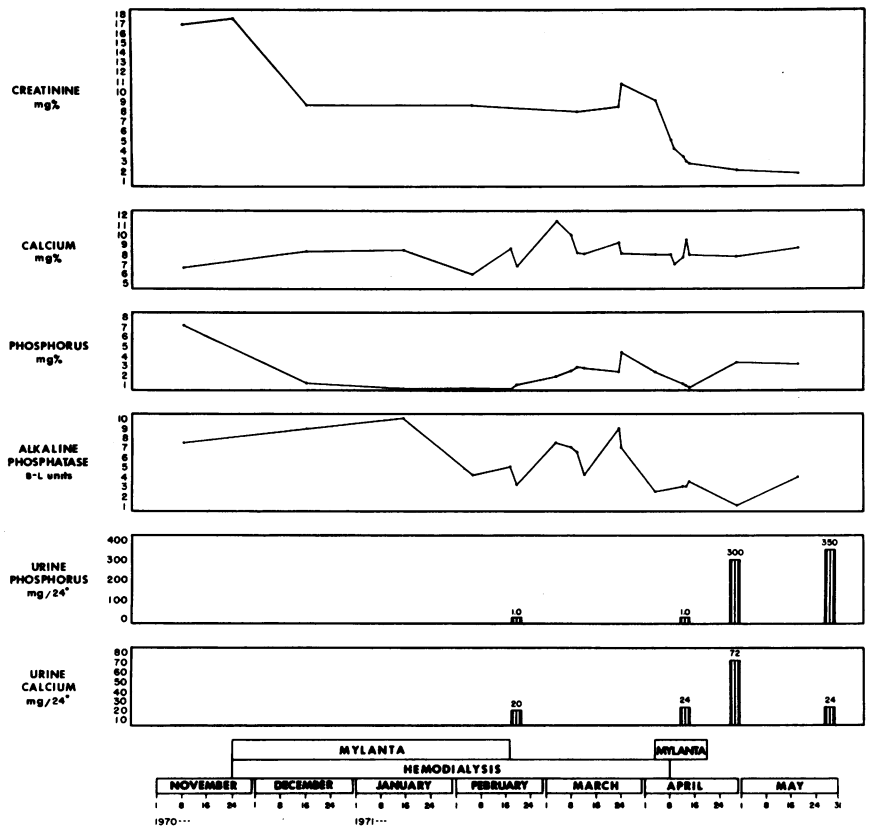

Chart 1.—Clinical course of patient with antacid-induced hypophosphatemia syndrome.

of blood, the hematocrit 27 percent, and leukocyte count, 7,800 per cu mm. The urine pH was 7.0, specific gravity 1.008 and the albumin reaction 2+. Microscopic examination of a centrifuged specimen showed 9 to 12 red blood cells and 1 to 2 leukocytes per high-power field, but no casts or crystals. No organisms grew on a culture of urine. The serum creatinine was 9.8 mg, uric acid 9.6 mg, serum albumin 3.2 grams, globulin 3.4 grams, alkaline phosphatase 3.5 Bessy-Lowry units, calcium 7.6 mg, phosphorus 5.5 mg and blood urea nitrogen 55 mg per 100 ml. Sodium content was 143 mEq, potassium 4.9 mEq and bicarbonate 21 mEq per liter.

An x-ray film showed slight cardiac enlargement and patchy infiltrates in both lower lung fields. Sinus rhythm with inverted T-waves in leads I, II, AVL and V 3-6 were shown on an electrocardiogram. An intravenous pyelogram showed the kidneys as small and contracted, each measuring 10 cm longitudinally. The calyceal system was not visualized.

The patient was treated with digoxin, furosemide, bed rest and a 40 mEq sodium diet. The clinical course is shown in Chart 1.

The patient was observed periodically over the succeeding five months while taking allopurinal, furosemide and ferrous sulfate. Hemodialysis was begun in November 1970 when serum creatinine was 16.9 mg per 100 ml; and, since serum phosphorus was 8.0 mg per 100 ml before dialysis was begun, Mylanta® was prescribed (each tablet contains magnesium hydroxide, 200 mg; aluminum hydroxide, 200 mg; and simethicone, 20 mg). The patient was treated for five hours, three times weekly, with a high performance parallel plate hemodialyzer.* After approximately six weeks of maintenance hemodialysis and Mylanta therapy, it was discovered that serum phosphorus had fallen to 2 mg per 100 ml (December 1970). Later the following month the patient began to complain of profound weakness and bone pain. She now walked with a waddling gait. Serum phosphorus was by then less than 0.5 mg per 100 ml and x-ray films of the pelvis showed a fracture of the inferior ramus of the ischium (Figure 1). Although this lesion had not been appreciated when the patient was initially evaluated in June 1970, in retrospect a pseudofracture in that location may well have been present. This finding

*D 4 Parallel Plate Dialyzer, manufactured by Life Med Division, American Hospital Supply.

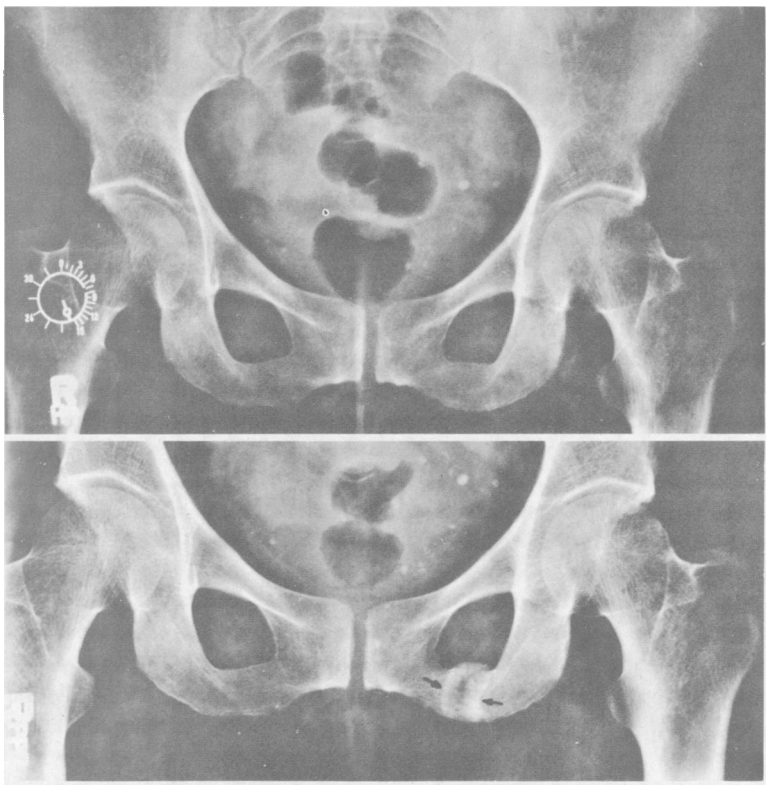

Figure 1.—The top photograph was taken in July, 1970; the bottom photograph in January, 1971. A fracture of the left inferior ramus of the pubic bone is seen in the bottom photograph. A pseudofracture in the same location can be discerned in the earlier film.

together with the low calcium-phosphorus ion product was felt to be diagnostic of osteomalacia underlying the patient's condition at the time of the bone fracture.

On further questioning the patient said that she had taken Mylanta in amounts up to 75 tablets daily. She gave a history of having eaten clay, sand and adobe periodically since childhood. The Mylanta tablets gave the patient a certain satisfaction, reminiscent of the sensation she derived from pica. Mylanta was discontinued in mid-February 1971, and the serum phosphorus then rose toward the levels usually seen in patients on maintenance hemodialysis. In addition, the patient gained strength, increased her activity and no longer complained of bone pain. The following month the patient underwent cadaveric renal homotransplantation, and Mylanta was given again as a prophylactic agent against peptic ulceration, since corticosteroids were being given for immunosuppression. Despite careful instructions given to the patient for the use of Mylanta during this period, the urinary phosphorus fell to less than 50 mg daily and hypophosphatemia recurred (serum phosphorus 0.7 mg per 100 ml). A rib biopsy revealed severe osteomalacia. Figure 2 shows the changes demonstrable in a decalcified specimen by use of an azan stain compared with the changes seen with an ordinary hematoxylin and eosin stain.[10] Osteoid stains blue with the azan stain. (In the photograph here shown it is the light gray area around the Haversian canal.) After Mylanta was discontinued, the phosphorus level became normal.

Discussion

Phosphorus depletion induced by ingestion of antacid preparations has been reported in four cases without azotemia,[11-14] and in four cases with renal failure.[1-3] In two cases the patients were undergoing maintenance hemodialysis, but there was no mention of bone abnormalities. In the present case a fracture developed and there was biopsy evidence of osteomalacia. Furthermore, muscle weakness, anorexia and mental depression developed after phosphate depletion from antacids while the patient was undergoing maintenance hemodialysis. The recognition of this syndrome in patients on maintenance hemodialysis is especially important in view of the widespread use of nonabsorbable antacids among them. One of the previously mentioned reports[2] indicated that erythrocyte adenosine triphosphate (ATP) depletion may be induced by antacid-induced phosphate de-

pletion, and that the loss of intracellular ATP could be responsible for the clinical syndrome associated with phosphorus deficiency. Bone lesions were not reported in that case, however.

Osteodystrophy in patients receiving maintenance hemodialysis is a widely recognized disorder, and osteomalacia and osteitis fibrosa, occurring singly and together, have been reported in such patients.[8,15,16] Therefore, the occurrence of osteomalacia itself is not surprising,[11] but a spontaneously developing pelvic fracture is unusual. Pendras[6] reported a spontaneous hip fracture in one of his patients on maintenance hemodialysis, but there was no mention of serum phosphorus content or of histologic examination of bone, nor was there an indication that the patient was taking non-absorbable antacids. In the case reported herein, since the fracture was through what was probably a pre-existing pseudofracture, it is likely that the antacid-induced phosphate deficiency aggravated the osteomalacia and increased the hazard of fracture.

Monitoring the serum phosphorus at bimonthly or monthly intervals is important when a patient on maintenance hemodialysis is being treated with non-absorbable antacids.[17] Furthermore, as suggested by Alfrey,[18] aluminum phosphate might be substituted for other antacids postoperatively in transplant patients if the serum phosphorus falls below normal. The combination of corticosteroids, with their osteoporotic effect, and low serum phosphorus would predispose to fractures.

Summary

A patient receiving maintenance hemodialysis treatment was twice found to have serum phosphorus of less than 1.0 mg per 100 ml, associated with symptoms of bone pain, weakness and waddling gait. The patient was found to have been ingesting large quantities of an antacid preparation containing aluminum hydroxide. When that was discontinued, serum phosphorus returned to normal levels.

At the time of maximum depression of the serum phosphorus a spontaneous fracture of the ischium was detected. Twelfth rib biopsy was performed during the second episode of profound hypophosphatemia. Hematoxylin and eosin as well as azan stains of the rib sections demonstrated profound osteomalacia. Previous reports of the phosphorus depletion syndrome in experimental animals as well as man have mentioned osteomalacia as a concomitant feature. In renal failure where osteomalacia is already a frequent complication, care must be taken not to aggravate this tendency by permitting phosphorus depletion through the use of these antacid preparations.

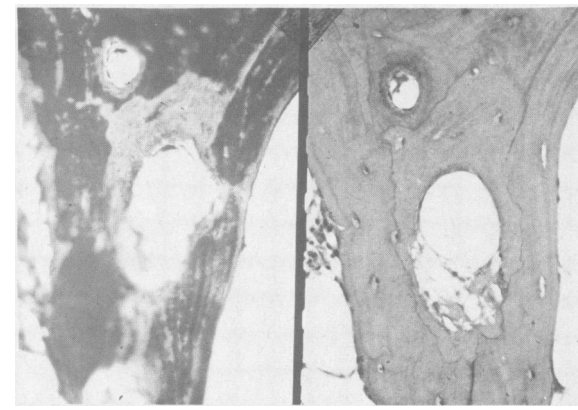

Figure 2.—These bone sections were taken from adjacent slices and stained with azan (left side) and hematoxylin and eosin (right side) respectively. Osteomalacia is identified in the azan stained specimen by the lightly stained area extending eccentrically around the central canal and along the bone margins. This is less clearly seen in the H & E stained specimen.

REFERENCES

1. Dodge WF, Travis L: Iatrogenic hypophosphatemia in infants with renal insufficiency. Ped 35:792-794, May 1965

2. Lichtman MA, Miller DR, Freeman RB: Erythrocyte adenosine triphosphate depletion during hypophosphatemia in a uremic subject. N Engl J Med 280:240-244, Jan 1969

3. Boelens PA, Norwood WK, Kjellstrand C, et al: Hypophosphatemia with muscle weakness due to antacids and hemodialysis. Am J Dis Child 120:350-353, Oct 1970

4. Dent CE: Rickets and osteomalacia from renal tubule defects. J Bone & Joint Surg 34B:266-274, May 1952

5. Lotz M, Zisman E, Bartter FC: Evidence for a phosphorus-depletion syndrome in man. N Engl J Med 278:409-415, Feb 1968

6. Pendras JP, Erickson RV: Hemodialysis: A successful therapy for chronic uremia. Ann Int Med 64:293-311, Feb 1966

7. Follis RH Jr, Jackson DA: Renal osteomalacia and osteitis fibrosa in adults. Bull Johns Hopkins Hosp 72:232-241, Apr 1943

8. Duursma SA, Visser WJ, Njio L: A quantitative histologic study of bone in 30 patients with renal insufficiency. Calc Tiss Res 9:216-225, 1972

9. Standbury SW, Lund GA: Parathyroid function in chronic renal failure. Quart J Med 35:1-23, Jan 1966

10. Bartelheimer H, Schmitt-Rohde JM: Die Biopsie des Knochens als differential diagnostische klinische Methode. Klinische Wochenschrift 35:429-440, May 1957

11. Bloom WL, Flinchum D: Osteomalacia with pseudofractures caused by the ingestion of aluminum hydroxide. JAMA 174:1327-1330, Nov 1960

12. Lotz M, Ney R, Bartter FC: Osteomalacia and debility resulting from phosphorus depletion. Trans A Am Physicians 77: 281-295, 1964

13. Ludwig GD, Kyle GC, de Blanco M: "Tertiary" hyperparathyroidism induced by osteomalacia resulting from phosphorus depletion. AM J Med 43:136-140, Jan 1967

14. Ansari A: Antacid-induced phosphorus depletion and repletion. Minn Med 53:837-838, Aug 1970

15. Jowsey J, Massrey SG, Coburn JW, et al: Microradiographic studies of bone in renal osteo dystrophy. Arch Intern Med 124: 539-543, Nov 1969

16. DeVeber GA, Oreopoulos DG, Rabinovich S, et al: Changing patterns of renal osteodystrophy with chronic hemodialysis. Trans Am Soc Artif Intern Organ 15:479-485, 1970

17. Goldsmith RS, Furszyfer J, Johnson WJ, et al: Control of secondary hyperparathyroidism during long term hemodialysis. Am J Med 50:692-699, May 1971

18. Alfrey AC, Jenkins D, Groth CG, et al: Resolution of hyperparathyroidism renal osteodystrophy and metastatic calcification after renal homotransplantation. N Engl J Med 279:1349-1356, Dec 1968