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Hepatic Osteodystrophy after Liver Transplantation in a Patient with Primary Biliary Cirrhosis

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A patient is presented who developed hepatic osteodystrophy after orthotopic liver transplantation in association with persistently low serum 25-hydroxyvitamin D levels. After successful liver transplantation there was a delay in the return to normal of the serum 25-hydroxyvitamin D levels until oral supplementation with vitamin D was instituted. This case emphasizes the need for effective treatment of hepatic osteodystrophy with vitamin D especially in patients considered for transplantation.

INTRODUCTION

Recent studies have shown that intramuscular 1-25-dihydroxyvitamin D (1), oral 1α-hydroxyvitamin D_3 (2), oral 25-hydroxyvitamin D_3 (3), and frequent large intramuscular doses of vitamin D_2 (4, 5) may heal the bone lesions associated with primary biliary cirrhosis. The patient presented here had progressive primary biliary cirrhosis and was treated with large daily doses of oral vitamin D before the development of bone symptoms. After hepatic transplantation for severe liver disease vitamin D was stopped because vitamin D metabolism was presumed to be normal. Three months after transplantation, the patient developed severe bone pain and multiple compression fractures of the spine despite apparent normal liver function. Her symptoms improved dramatically after 6 wk of oral vitamin D therapy. Levels of 25-hydroxyvitamin D were measured on frozen serum samples obtained throughout the 18 months before and 3 yr after transplantation.

CASE REPORT

The patient first presented to The Mary Imogene Bassett Hospital in July 1976 at age 46 with painless jaundice. She had had a cholecystectomy performed elsewhere in 1970 for gallstones.

Initial physical examination revealed jaundice and a slightly enlarged liver. Serum enzymes showed an alkaline phosphatase of 1225 U/L (normal 30–100), bilirubin of 133 mol/L (7.7 mg/100 ml), and a serum glutamate oxaloacetate transaminase of 167 U/L (normal 0–40). Antimitochondrial antibody was positive at a 1:160 di-

lution. A normal pancreatic duct and a normal biliary tree were demonstrated by endoscopic retrograde cholangiopancreatography. Liver biopsy interpretation was consistent with primary biliary cirrhosis.

By early 1977, therapy included cholestyramine, medium-chain triglyceride dietary supplementation, and 1.25 mg of oral vitamin D_2 each day. In June 1977, the patient developed melena but upper gastrointestinal series, barium enema, colonoscopy, and gastroscopy showed only duodenitis. She was treated initially with 2 oz of Amphogel daily and subsequently with Mylanta, 2–4 oz daily. This was continued after transplantation. In December 1977, her itching became unbearable and methyltestosterone was administered with dramatic improvement in this symptom. In March 1978, she developed mild pain in the bones of the lower legs; the dose of oral vitamin D_2 was increased to 1.25 mg daily alternated with 2.5 mg, and a single intramuscular dose of vitamin D_2 (1.25 mg) was administered. At this time, her serum bilirubin had reached 879 mol/L (51 mg/100 ml), serum cholesterol was decreasing, and xanthomatous skin deposits were regressing. Because of these ominous signs, it was decided to attempt liver transplantation. Further intramuscular vitamin D_2 was not given. No corticosteroids were given before transplantation.

In June 1978, liver transplantation was performed at the University of Colorado. At discharge, her immunosuppression consisted of prednisone 30 mg in divided doses and azathioprine 100 mg. In September 1978, she developed back pain attributed to compression fractures of her spine. At the same time, her serum alkaline phosphatase and glutamate oxaloacetate transaminase became markedly elevated (Fig. 1). It was presumed that she was undergoing a rejection reaction, and large doses of corticosteroids were given. At the same time, her serum first became positive for hepatitis B surface antigen. Her serum glutamate oxaloacetate transaminase level decreased to the levels seen before the "rejection" but the serum alkaline phosphatase continued to be markedly elevated. Heat fractionation of the serum alkaline phosphatase suggested a major origin of the enzyme from bone. In November, alkaline phosphatase was 402 U/L and heated alkaline phosphatase was 154
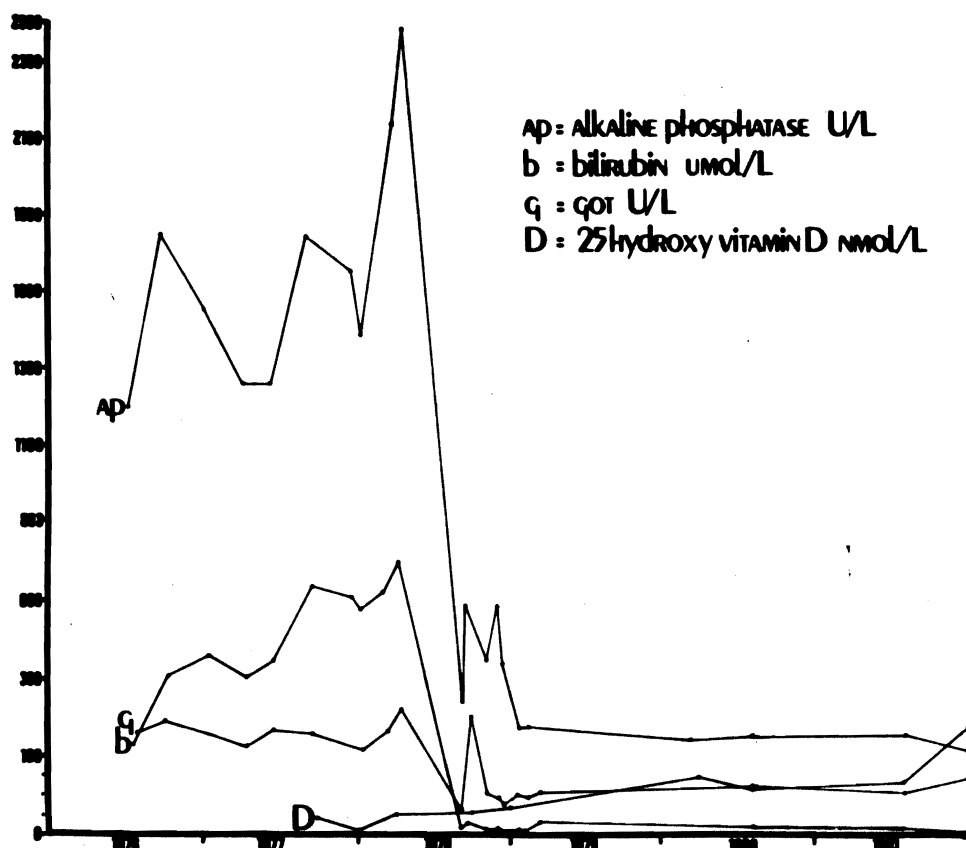
FIG. 1. Laboratory studies 18 months before transplantation and 3 yr after transplantation. (Conversion SI to traditional units: serum bilirubin 1 mol/L 0.058 mg/100 ml, 25-hydroxyvitamin D 1 nmol/L 0.4 ng/ml). Normal ranges: 25-hydroxyvitamin D 25–138 nmol/L, bilirubin 0–17 mol/L, alkaline phosphatase 30–100 units/L, serum glutamate oxaloacetate transaminase (GOT) 0–40 units/L. Liver transplantation took place in June 1978.

U/L. In December, alkaline phosphatase was 393 U/L and heated alkaline phosphatase was 193 U/L. Oral vitamin D_2 1.25 mg twice a week and calcium 1.0 g/day were begun. After 6 wk, the serum alkaline phosphatase level decreased and her generalized bone pain, which had become quite severe involving primarily the ribs and sternum, subsided. Oral vitamin D_2 at 1.25 mg/wk has been continued to date (September 1982) with the patient free of bone pain since February 1979. She continues to do well with maintenance immunosuppression of 22.5 mg of prednisone in one dose and 100 mg of azathioprine as of September 1982. Figures 2 to 5 illustrate bony demineralization, compression fractures of the spine, and fracture of the sternum consistent with metabolic bone disease. They also show the development of curvature of the sternum consistent with osteomalacia.

Laboratory studies illustrating the clinical course are shown in Figure 1. Specific 25-hydroxyvitamin D levels are shown in Table 1. During the patient's entire period of observation from July 1976, her serum calcium and phosphate levels have remained in a normal range. The range for calcium was 8.9–9.7 mg/dl and phosphate 2.4–3.9 mg/dl. Only one phosphate determination was 2.4 mg/dl. Her antimitochondrial antibody was negative

5 months after transplantation but was again positive in August 1980 (1:640 titer).

Hepatic chemistries were measured by standard autoanalyzer techniques. Determination of 25-hydroxyvitamin D levels was accomplished on serum samples preserved at −20°C using a commercially available competitive protein binding assay based on Haddad's methods (6).

DISCUSSION

Hepatic osteodystrophy is a general term that describes the metabolic bone disease found in certain cases of chronic liver disease. This disorder is most clearly manifested in patients with primary biliary cirrhosis. Histologically, the findings are those of both osteomalacia and osteoporosis. The osteomalacia is not usually associated with either hypocalcemia or with secondary hyperparathyroidism (1, 7). The pathogenesis of this metabolic bone disease is not entirely clear. Abnormalities of vitamin D metabolism have been implicated (1, 5), since 25-hydroxyvitamin D, the major circulating form of vitamin D, is synthesized mainly in the liver of humans. Serum levels of 25-hydroxyvitamin D have been found

FIG. 2. Lateral chest x-ray June 1978 prior to transplantation showing a structurally normal sternum and demineralization of the spine.

to be reduced in some patients with severe primary biliary cirrhosis with the bone lesions of hepatic osteodystrophy (5) and normal in some others (1). Possible reasons for decreased 25-hydroxyvitamin D levels are decreased hepatic 25-hydroxylation of vitamin D, malabsorption of vitamin D, and increased urinary losses of vitamin D or of its metabolites (8, 9).

Studies have demonstrated that the osteomalacia associated with hepatic osteodystrophy does respond to vitamin D therapy in some instances (1–5). Skinner *et al.* (5) found that serum 25-hydroxyvitamin D concentrations could be raised if large doses of vitamin D were provided with monthly intramuscular injections. Most studies have suggested that patients with primary biliary cirrhosis are capable of making at least some 25-hydroxyvitamin D from very large parenteral doses (10).

Low serum levels of 25-hydroxyvitamin D were present in this patient before hepatic transplantation. This occurred despite the oral intake of 1.25 mg of vitamin D_2 daily for 18 months. With progression of the liver disease, she began to develop bone pain 2 months before transplantation. At this time her serum vitamin D level was 22.5 nmol/L (normal 25–138). A single parenteral dose of vitamin D_2 was given shortly before orthotopic liver transplantation (11, 12).

No supplemental vitamin D was administered in the immediate posttransplantation period. Three months after transplantation, at the time of development of severe bone pain and vertebral collapse, serum 25-hydroxyvitamin D levels continued to be low (Fig. 1 and Table 1).

When bone pain developed 3 months after transplantation, 1.25 mg of vitamin D_2 given orally twice weekly led to relief of bone pain and lowered serum alkaline phosphatase levels. Six weeks after concluding a course of vitamin D_2 1.25 mg, twice weekly, the 25-hydroxyvitamin D level remained low even though clinical improvement was apparent (Table 1).

This patient's bone symptoms may have been in part due to osteoporosis, but the severe clinical manifestations of rib and sternal pain, the apparent response to vitamin D, as well as the deformity which developed in the sternum, suggest that the osteomalacia of hepatic osteodystrophy played a major role in this patient's bone disease. Bone biopsies are not available to confirm this.

The bone disease in this woman was undoubtedly multifactorial. She took antacids before and after the transplantation. Antacids may cause phosphate malabsorption which can then lead to osteomalacia (13). However, her serum phosphate levels were normal repeatedly,

FIG. 3. Lateral chest x-ray December 1978 showing compression fractures of the spine.

This patient's course suggests that patients who might not ordinarily survive their liver disease to develop hepatic osteodystrophy, if treated with liver transplantation may develop severe bone complications. This complication might be prevented if careful attention is paid to vitamin D treatment. In those patients on corticosteroids vitamin D therapy may also improve or delay bone changes seen with glucocorticoid-induced osteopenia (19).

FIG. 4. Lateral chest x-ray March 1979 showing healed sternal fracture and increased curvature of the sternum.

FIG. 5. Lateral chest x-ray January 1981 showing increased mineralization of the spine (healed sternal fracture and sternal curvature similar to March 1979).

with one exception of a value of 2.4 mg/dl, so that osteomalacia solely due to antacid ingestion seems unlikely, but it may have been a contributing factor.

The exact role of vitamin D metabolites in the mineralization of bone is not known (14). Normal levels of 1-25 dihydroxyvitamin D have been reported in patients with osteomalacia (15). Since 25-hydroxyvitamin D is the major circulating form of vitamin D, a vitamin D depleted state was present before transplantation, as documented by low 25-hydroxyvitamin D levels done on frozen serum samples retrospectively (Table 1). This may have been due to malabsorption and possible decreased 25-hydroxylation. Use of Questran may also have contributed to the loss of vitamin D by binding vitamin D and interrupting the enterohepatic circulation of vitamin D. Postoperatively the patient had a prolonged hospitalization with absent sun exposure, and vitamin D stores were not replaced pharmacologically. Corticosteroid therapy may also alter vitamin D metabolism and lead to depressed 25-OH vitamin D levels (16) by metabolism of 1-25 dihydroxyvitamin D (17, 18) to a more polar, biologically inactive metabolite. These effects on vitamin D metabolism may then lead to decreased intestinal Ca^{++} absorption (17, 18).

TABLE 1
25-Hydroxyvitamin D Levels

	25-Hydroxyvitamin D (n = 25–138 nmol/L)
September 1977	17.5
January 1978	7.5
March 1978	22.5
September 1978	25
January 1979	30
March 1980	70
August 1980	55
February 1981	70
July 1981	156

REFERENCES

1. Long RG, Varghese Z, Meinhard EA, et al. Parenteral 1,25-dihydroxycholecalciferol in hepatic osteomalacia. Br Med J 1978;1:75-7.
2. Compston JE, Crowe JP, Horton LWL. Treatment of osteomalacia associated with primary biliary cirrhosis with oral 1-alpha-hydroxyvitamin D_3. Br Med J 1979;2:309.
3. Reed JS, Meredith SC, Nemchausky BA, et al. Bone disease in primary biliary cirrhosis: reversal of osteomalacia with oral 25-hydroxyvitamin D. Gastroenterology 1980;78:512-17.
4. Compston JE, Horton LWL, Thompson RPH. Treatment of osteomalacia associated with primary biliary cirrhosis with parenteral vitamin D_2 or oral 25-hydroxyvitamin D_3. Gut 1979;20:133-6.
5. Skinner RK, Long RG, Sherlock S, et al. 25 hydroxylation of vitamin D in primary biliary cirrhosis. Lancet 1977;1:720-1.
6. Haddad JG. Competitive protein binding radioassay for 25 hydroxycholecalciferol. J Clin Endocrinol Metab 1971;33:992-5.
7. Long RG. Hepatic osteodystrophy: outlook good but some problems unsolved. Gastroenterology 1980;78:644-7.
8. Krawitt EL, Grundman KJ, Mawer EB. Absorption, hydroxylation, and excretion of vitamin D_3 in primary biliary cirrhosis. Lancet 1977;2:1246-9.
9. Barragry JM, Long RG, France MW. Intestinal absorption of cholecalciferol in alcoholic liver disease and primary biliary cirrhosis. Gut 1979;20:559-64.
10. Meredith SC, Rosenberg IR. Gastrointestinal-hepatic disorders and osteomalacia. Clin Endocrinol Metab 1980;9:131-50.
11. Starzl TE, Koep LJ, Halgrimson CG, et al. Fifteen years of clinical liver transplantation. Gastroenterology 1979;77:375-88.
12. MacDougall BRD, Calne RY, McMaster P, et al. Survival and rehabilitation after orthotopic liver transplantation. Lancet 1980;1:1326-8.
13. Insogna KL, Bordley DR, Caro JF, et al. Osteomalacia and weakness from excessive antacid ingestion. JAMA 1980;244:2544-6.
14. Arnaud SB. 25-Hydroxyvitamin D_3 treatment of bone disease in primary biliary cirrhosis. Gastroenterology 1982;83:137-42.
15. Eastwood JB, de Wardener HE, Gray RW, et al. Normal plasma $-1,25-(OH)_2$-Vitamin-D concentrations in nutritional osteomalacia. Lancet 1979;1:1377-8.
16. Klein RG, Arnaud SB, Gallagher JC, et al. Intestinal calcium absorption in exogenous hypercortisonism. Role of 25-hydroxyvitamin D and corticosteroid dose. J Clin Invest 1977;60:253-9.
17. Carre M, Ayigbede O, Miravet L, et al. The effect of prednisolone[R] upon the metabolism and action of 25-hydroxy and 1,25-dihydroxyvitamin D_3. Proc Nat Acad Sci USA 1974;71:2996-3000.
18. Avioli LV, Birge SJ, Lee SW. Effects of prednisone on vitamin D metabolism in man. J Clin Endocrinol Metab 1968;28:1341-6.
19. Hahn TJ, Halstead LR, Teitelbaum SL, et al. Altered mineral metabolism in glucocorticoid-induced osteopenia. Effect of 25-hydroxyvitamin D administration. J Clin Invest 1979;64:655-65.