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CASE REPORT

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A patient with symptomatic osteomalacia associated with Fanconi syndrome

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Abstract We report a patient with renal tubulointerstitial fibrosis and symptomatic osteomalacia associated with Fanconi syndrome. A 55-year-old woman was hospitalized because of an inability to walk. Beginning approximately 2 years previously, she had experienced gradually worsening pain in the hips, shoulders, and trunk, culminating in a bedridden state. Serum urea nitrogen was 38 mg/dl; creatinine, 2.6 mg/dl; uric acid. 3.6 mg/dl; phosphate, 2.3 mg/dl; and alkaline phosphatase, 2111 IU/l. Urinary β2 microglobulin was 72 331 μg/day. Aminoaciduria, renal glucosuria, and proximal renal tubular acidosis with a normal anion gap were also noted. The patient was diagnosed with Fanconi syndrome. Radiography demonstrated typical Looser zones in the proximal portion of the left and especially the right femoral shaft, and at several other sites. A renal biopsy specimen disclosed severe tubulointerstitial fibrosis with little cellular infiltration. Glomeruli were largely intact. A bone biopsy specimen indicated osteomalacia; no tetracycline labeling could be seen along most trabecular bone surfaces, and the ratio of total osteoid volume to bone volume was increased (71.8%). Bicarbonate administration (9 g/day) gradually lessened most symptoms, permitting ambulation. Calcitriol administration decreased excessive intact-parathyroid hormone emerging after 2 months of acidosis correction. Thus, severe acidosis associated with Fanconi syndrome can induce osteomalacia showing serious skeletal complications, but also responsiveness to bicarbonate therapy.

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Introduction

Osteomalacia is a disorder characterized by decreased bone mineralization resulting in increased osteoid volume. Decreased mineralization in young patients causes rickets, reflecting to damage to growth plates (epiphyses). In older individuals whose epiphyses have closed, defective mineralization causes osteomalacia. Radiographically, typical osteomalacia associated with difficult ambulation had shown Looser zones, which have become rare in recent years in regions where medical care and nutrition have improved. An exception has been reported in association with monoclonal gammopathies including multiple myeloma and lymphoma.[1]

Here, we report the rare occurrence of symptomatic, typical osteomalacia associated with idiopathic Fanconi syndrome. Radiographically, Looser zones were demonstrated and a bone biopsy specimen showed greatly increased osteoid volume.

Case report

A 55-year-old woman was admitted to our institution for diagnostic evaluation of an inability to walk on October 22, 2002. Beginning in 2000, pain became apparent in the hips, shoulders, and trunk, progressing gradually until August 2002, when she could no longer walk without the assistance of another person, and appetite loss and vomiting became prominent. Despite the patient's bedridden state, she had not consulted any physician, and had not taken any medicine. She had no family history of any similar illness.

On admission the patient was 153 cm tall and weighed 34 kg. Blood pressure was 128/66 mmHg. The thorax showed severe deformity. She complained of severe pain in

the hip joints, especially on the right, as well as in the shoulders and trunk. She had difficulty arising from a seated or recumbent position. Mild edema was evident in the lower extremities. Proximal muscle weakness associated with wasting was apparent in the upper and lower extremities.

Hematologic findings were: erythrocyte count, 2.46×10^6/μl; hemoglobin (Hb), 7.1 g/dl; hematocrit, 22.7%; reticulocytes, 1.9×10^4/μl; leukocytes, 3300/μl; and platelets, 10.4×10^4/μl. In serum biochemical analysis, total protein was 6.5 g/dl; albumin, 3.2 g/dl; urea nitrogen (UN), 38 mg/dl; creatinine (Cr), 2.6 mg/dl; and uric acid (UA), 3.6 mg/dl. Sodium was 148 mmol/l; potassium, 4.5 mEq/l; chloride, 116 mmol/l; calcium, 4.2 mEq/l; and phosphate, 2.3 mg/dl. Aspartate aminotransferase (AST) was 28 IU/l; alamine aminotransferase (ALT), 32 IU/l; alkaline phosphatase (ALP), 2111 (IU/l) (predominantly the bone-type isoenzyme); γ-glutamyltransferase (GTP), 22 IU/l; and lactate dehydrogenase (LDH), 164 IU/l. Serum cadmium and lead concentrations were less than 0.4 μg/dl and 3.0 μg/dl, respectively. Fasting blood glucose was 75 mg/dl, and Hb A1c was 4.2%. C-reactive protein (CRP) was not detected, the erythrocyte sedimentation rate (ESR) was 25 mm/h. On endocrinologic evaluation, the plasma renin concentration was 6.9 pg/ml; aldosterone, 18.6 ng/dl; intact-parathyroid hormone (i-PTH), 184 μg/ml; $1,25(OH)_2$vitamin D3 concentration, below 6.0 ng/l; 25(OH) vitamin D, 11.5 μg/l; and bone gla protein (BGP), 111 ng/ml.

On immunologic evaluation, immunoglobulin(Ig)G was 1220 mg/dl; IgA, 158 mg/dl; IgM, 140 mg/dl; and IgE, 10 U/ml. Fifty percent hemolytic unit of complement (CH_{50}) was 36 U; C3 concentration, 60 mg/dl; and C4 concentration, 18 mg/dl. Antinuclear antibody (detected by an immunofluorescence method using Hep-2 cells), anti-DNA antibody, and antiribonucleoprotein (RNP) were not detected.

On arterial blood gas analysis, pH was 7.16; pO_2, 119 torr; pCO_2, 24 torr; and bicarbonate (HCO_3^-), 8 mmol/l. On urinalysis, pH was 5.0; glucose, 3+; protein, 1+; and occult blood, −. The urinary sediment contained fewer than 1 erythrocyte per high-power field (HPF). No Bence–Jones protein was detected. In a 24-h urine collection, glucose was 4.9 g/day; protein, 0.75 g/day; β2 microglobulin (MG), 72 731 μg/day; and *N*-acetyl-D-glucosaminidase (NAG), 4 IU/day. Amino acid analysis in urine indicated abnormal excretion of 14 different amino acids. Creatinine clearance was 11.8 ml/min. Percent tubular resorption of phosphate (%TRP) was 42.0% (normal: 55–85). After the serum bicarbonate concentration was normalized by bicarbonate loading with 9 g/day, the highest urine pH was 8.5 (above 7.5); urine bicarbonate (HCO_3^-), 40 mEq/l; fractional excretion of bicarbonate (HCO_3^-), 24% (more than 15). Calculated by serum sodium-(chloride + bicarbonate), the anion gap was 14 (normal range, 10–14 mEq/l).

Computed tomographic and ultrasonographic examinations showed mild atrophy of the kidneys unassociated with calcification. Generalized aminoaciduria, renal glucosuria, hypophosphatemia, hypouricemia, and proximal tubular metabolic acidosis with a normal anion gap indicated the presence of Fanconi syndrome. Potential causative disorders such as multiple myeloma and intoxication with cadmium or lead were excluded.

Radiographs of the upper femoral shaft showed narrow radiolucent lines 2–4 mm in width with sclerotic borders, a pseudofracture pattern termed Looser zones, as well as thinning of the cortex associated with reduced bone density. Looser zones were bilateral, being more prominent on the right, symmetric in location, and perpendicular in orientation to the cortical margins of bones (Fig. 1a). This finding was apparent in the right clavicle and in multiple ribs, resulting in deformity of the thorax (Fig. 1b), showed by computed tomography to represent deviation of the sternum to the left (Fig. 1c). The pelvis was markedly deformed with multiple pseudofractures (Fig. 1d). Bone scintigraphy with ^{99m}Tc-labeled methylene diphosphonate (MDP) demonstrated intense uptake in regions of pseudofracture (Fig. 2). When bone mineral density (BMD) was measured by dual-energy X-ray absorptometry (DEXA), BMD in lumbar spine (L3), right forearm, and right hip were 0.40, 4.18, and 4.47 SD below the mean peak of normal bone mass (*z*-score), respectively.

On November 6, 2002, a right iliac bone biopsy was performed, 14 days after administration of tetracycline for double-labeling studies. Renal biopsy was performed on December 5, 2002.

Bone histology

Undecalcified thin sections 5 mm in thickness were prepared from bone specimens and stained by the Villanueva methods. Sections were observed with an epifluorescence microscope using ultraviolet excitation. In a portion of bone trabecula magnified at ×160, parameters were measured directly with an imageanalysis system linked to a microcomputer.

As shown in Fig. 3a, the bone biopsy specimen was diagnostic for osteomalacia, since no tetracycline labeling could be seen along most trabecular bone surfaces and osteoid volume was greatly increased [(osteoid volume/bone volume) × 100 = 71.8%; normal, 2.17 ± 1.14%], as were osteoid surface [(osteoid surface/bone surface) × 100 = 89.5%; normal, 16.7 ± 7.0%] and osteoid thickness, 83.2 μm; normal, 9.16 ± 2.0 (Fig. 3b,c). The ratio of total bone volume to total tissue volume was increased (43.0%; normal, 20.8% ± 1.5%). However, the ratio of fibrous tissue volume to total volume was increased (1.39%; normal, <0.5%), and the ratio of eroded surface to bone surface was increased (10.5%; normal, 5.6 ± 1.9%). Numbers of both osteoblasts and osteoclasts were increased in near the inside of a resorption cavity. Features of secondary hyperparathyroidism were also exhibited (Fig. 3d).

Renal histology

Light microscopic examination of a renal specimen containing eight glomeruli revealed global sclerosis in three, with the other five showing a mild increase in glomerular size but no mesangial cell proliferation (Fig. 4a). Marked atrophy

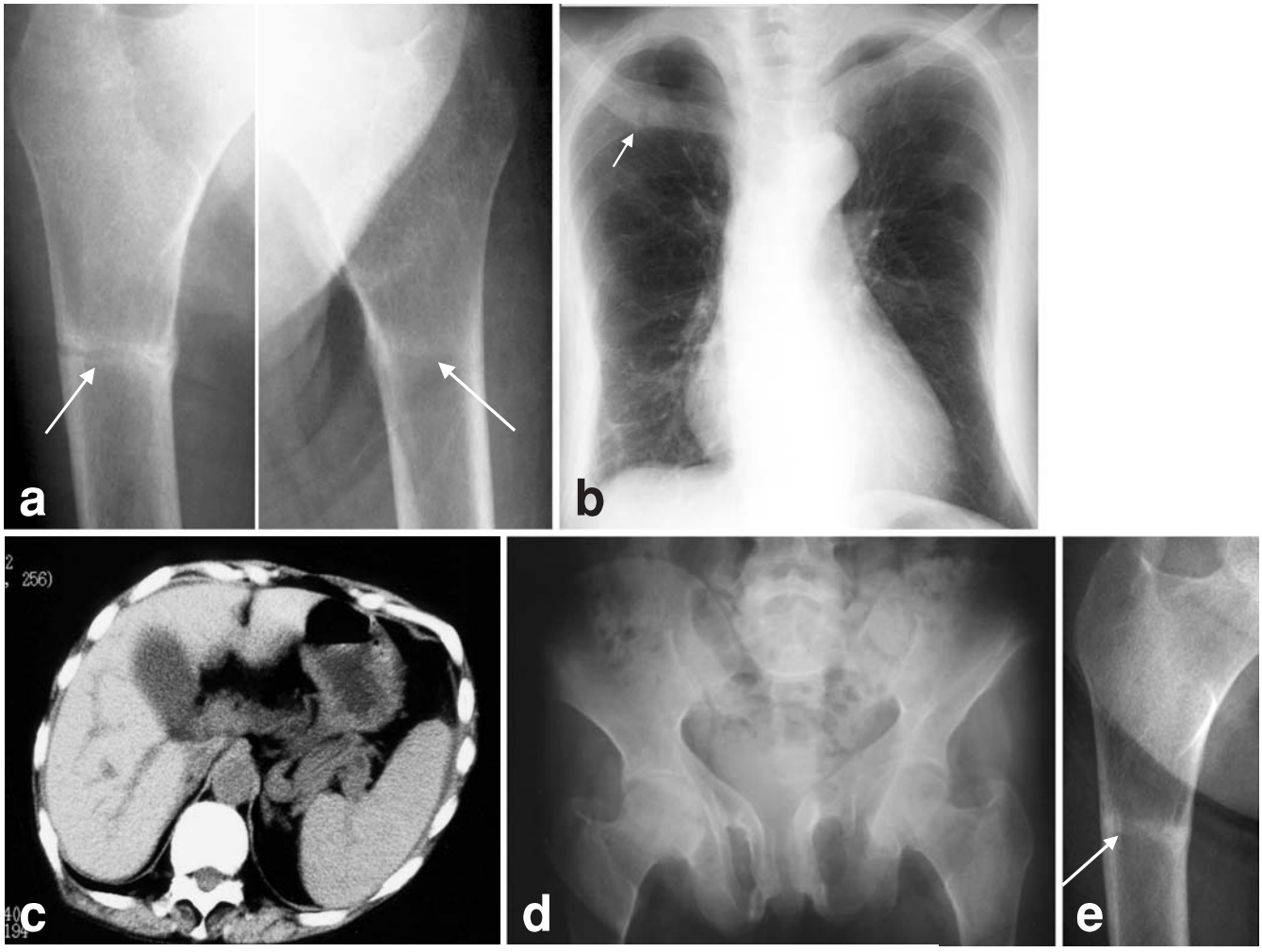

Fig. 1. a Radiographs of the upper femoral shaft show a pseudofracture pattern termed Looser zones (*arrows*), as well as thinning of the cortex associated with reduced bone density. Looser zones are bilateral, being more prominent on the right, symmetric in location, and perpendicular in orientation to the cortical margins of bones. **b** Looser zones are apparent in the right clavicle (*arrow*) and in multiple ribs resulting in deformity of the thorax. **c** Deformity of the thorax is shown by computed tomography to represent deviation of the sternum to the left. **d** The pelvis is markedly deformed with multiple pseudofractures. **e** The Looser zone in the proximal portion of the right femur (*arrow*) became indistinct on August 4, 2004

and destruction of both proximal and distal tubules as well as interstitial fibrosis were observed, but cellular infiltration was scant (Fig. 4b). Congo red staining was negative. Immunofluorescent examination did not show significant staining with immunoglobulins or complement components. Electron microscopic examination disclosed no electron-dense deposits. Tubulointerstitial fibrosis was diagnosed.

Clinical course

As the patient was diagnosed with Fanconi syndrome associated with proximal (type 2) renal tubular acidosis, sodium bicarbonate was started with an initial dose of 2 g/day, later increased to a maintenance dose of 9 g/day. Peripheral blood pH then increased to 7.41 with a serum bicarbonate (HCO_3^-) concentration of 24 mmol/l. Serum Cre was 3.0 mg/dl; phosphate, 3.0 mg/dl; %TRP, 22.9; and $1,25(OH)_2$vitamin D3 concentration, below 6.0 ng/l. Following administration of bicarbonate, most symptoms such as bone pain, muscle weakness, and anorexia improved gradually but steadily, permitting ambulation using a crutch after 3 months of therapy. However, intact PTH increased from 184 to 1037 pg/ml. Although four pieces of cervical parathyroid were detected by diagnostic imaging procedures using ^{99m}Tc-MIBI (methoxyl isobutyl isonitrile) scintigraphy, no parathyroid mass lesion was detected by ultrasonography. This indicates that parathyroid function was enhanced remarkably, but the parathyroid was not yet swollen. Accordingly, vitamin D3 derivative was administered at an initial dose of 0.5 μg/day beginning 2 months after initiating bicarbonate therapy, and increased to 1.5 μg/day after 4 months.

On August 4, 2004, s-UN was 44 mg/dl; Cr, 4.2 mg/dl; calcium, 4.6 mEq/l; and phosphate, 4.3 mg/dl. Arterial pH was 7.42 and HCO_3^-, 24 mmol/l. Intact PTH decreased to 375 pg/ml and ALP to 415 IU/l. The Looser zone in the proximal portion of the right femur became indistinct (Fig. 1e). Bone mineral density in the lumbar spine (L3), right

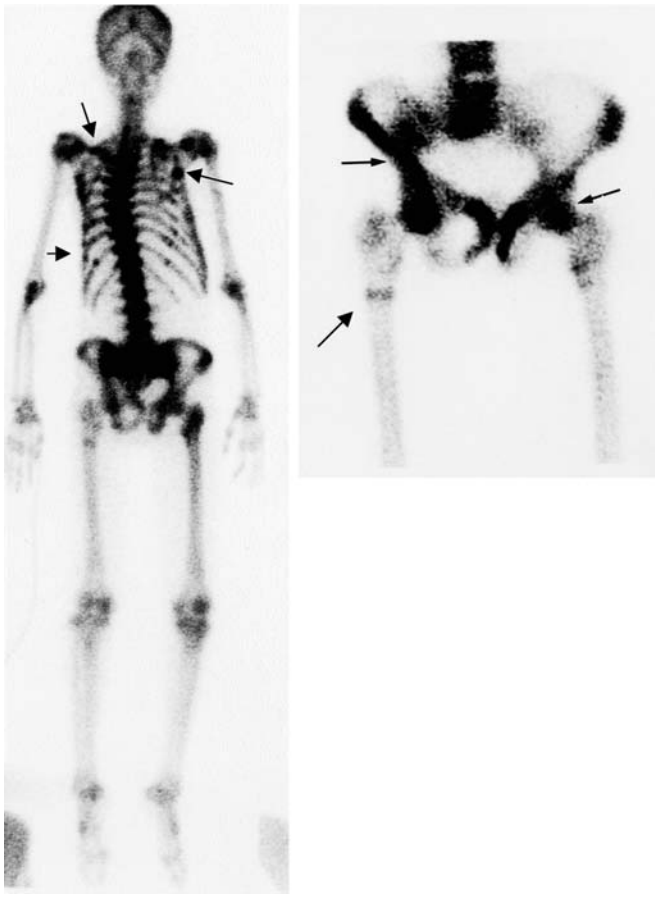

Fig. 2. Bone scintigraphy with ^{99m}Tc-labeled methylene diphosphonate demonstrated intense uptake in regions of pseudofracture (*arrows*)

forearm, and right hip were 1.03 above SD, 4.97 below SD, and 0.01 SD, respectively, below the mean peak for normal bone mass (z-score). These changes represented a mild increase, no change, and a marked increase, respectively.

Discussion

Osteomalacia, considered one of the low-turnover bone diseases, represents a defective mineralization of newly formed bone matrix. Causes of rickets in infants include genetically determined abnormalities of vitamin D metabolism such as vitamin D-dependent-rickets of types 1 and II, and hypophosphatemic vitamin D-resistant rickets.[2] Various other causes have been suggested for osteomalacia developing in older individuals. Dietary deficiency of vitamin D and decreased synthesis of vitamin D reflecting minimal exposure to sunlight once were common in bed-bound institutionalized patients. However, fortification of foods with vitamin D have greatly reduced incidence of osteomalacia arizing from these causes.[3] Osteomalacia also was reported in patients with gastrointestinal disease such as gastrectomy, celiac sprue, intestinal bypass, intestinal resection, chronic pancreatitis, and primary biliary cirrhosis.[4–6] Osteomalacia occurred in 43%–30% of patients after gastrectomy. Patients with a Billroth II gastrectomy were at a greater risk than those with a Billroth I procedure because of exclusion of the duodenum. Prevalence of osteomalacia from these causes also has declined because of medical awareness and nutritional assessment to ensure sufficient vitamin D despite malabsorption. In the long term, subclinical osteomalacia has been reported to be frequent in adult patients with nephrotic syndrome coexisting with generally normal renal function, reflecting increased urinary excretion of 25(OH) vitamin D; no skeletal abnormality was visible radiographically.[7] Drugs such as rifampicin, phenytoin, and phenobarbital also have been reported to induce osteomalacia, since they increase vitamin D catabolism via hepatic enzyme activation.[8,9]

Fanconi syndrome can be diagnosed when proximal-type renal tubular acidosis (type 2) is associated with generalized proximal tubular dysfunction such as glucosuria, phosphaturia, uricosuria, aminoaciduria, and tubular proteinuria. Fanconi syndrome also has been reported as a cause of osteomalacia. One possible etiology of Fanconi syndrome in acquired adulthood is monoclonal gammopathies, including those associated with multiple myeloma and lymphoma.[10,11] Exposure to cadmium or lead, as well as a history of treatment with ifosmide or cisplatin, should be considered. If these causes are ruled out, Fanconi syndrome is considered idiopathic. In this case, a low circulating level of $1,25(OH)_2D3$ was considered due to impaired renal production associated with renal failure, since serum 25(OH) vitamin D level was normal, though urinary excretion was not measured.

The specific radiographic hallmark of osteomalacia, referred to as Looser zones, is the presence of pseudofractures showing radiolucent bands 2–5 mm in width, with sclerotic borders. Usually oriented perpendicular to the bone surface, these are multiple, bilateral, and symmetrically located.[12] They most often are found at the femoral neck, medial aspect of the femoral shaft, pubis, ischial rami, ulna, scapula, clavicle, ribs, or metatarsals, showing increased uptake with ^{99m}Tc MDP bone scintigraphy.[13] Presently, however, Looser zones are detected only infrequently in patients clinically and histologically diagnosed with osteomalacia. Osteopenia and osteoporosis, evident as reduced bone density with thinning of the cortex, are the most common findings in patients with osteomalacia but are nonspecific, since they occur in other bone diseases. Brenner et al. reviewed skeletal radiographs in 92 patients with renal tubular acidosis, finding abnormalities only in patients with type 2 disorders including Fanconi syndrome. However, most of these patients had osteopenia without pseudofractures.[14]

Osteomalacia is confirmed by bone histomorphometric analysis when the zone of double tetracycline labeling along most trabecular bone surfaces is narrowed or inapparent, and the ratio of total osteoid volume to bone volume increases more than 10%. Active osteoblasts along trabecular bone surfaces usually are numerous in osteomalacia except when caused by adult hypophosphatemia, malnutrution, or renal osteodystrophy. Patients with vitamin D deficiency

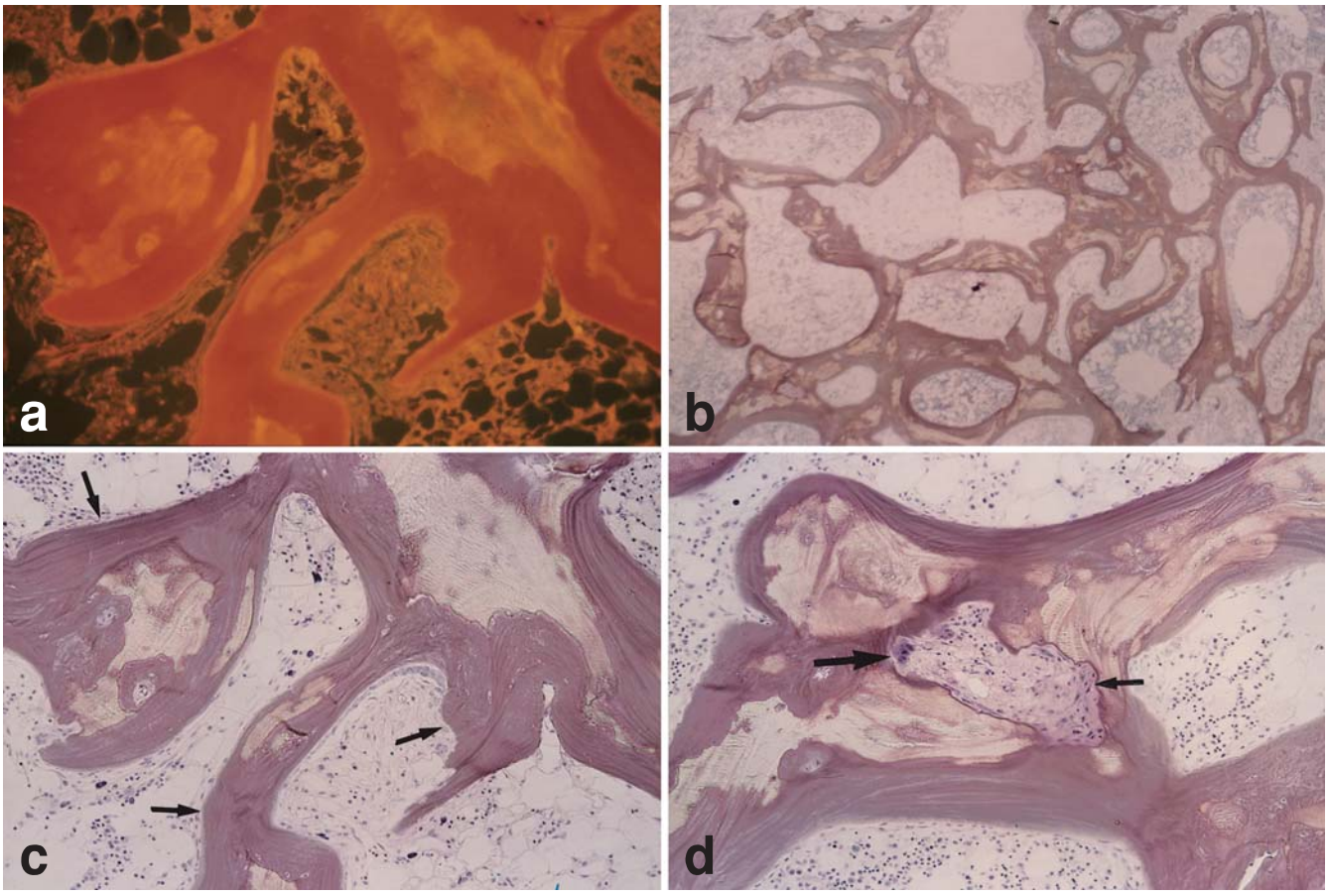

Fig. 3. **a** T fluorescence microscopy did not show labeling by tetracycline at most trabecular bone surfaces (×100). **b** Osteoid volume was greatly increased (Villanueva staining; ×20). **c** Osteoid volume (*arrows*) was greatly increased (Villanueva staining; ×100). **d** Numbers of both osteoblasts (*small arrow*) and osteoclasts (*large arrow*) were increased near the inside of a resorption cavity (Villanueva staining; ×100)

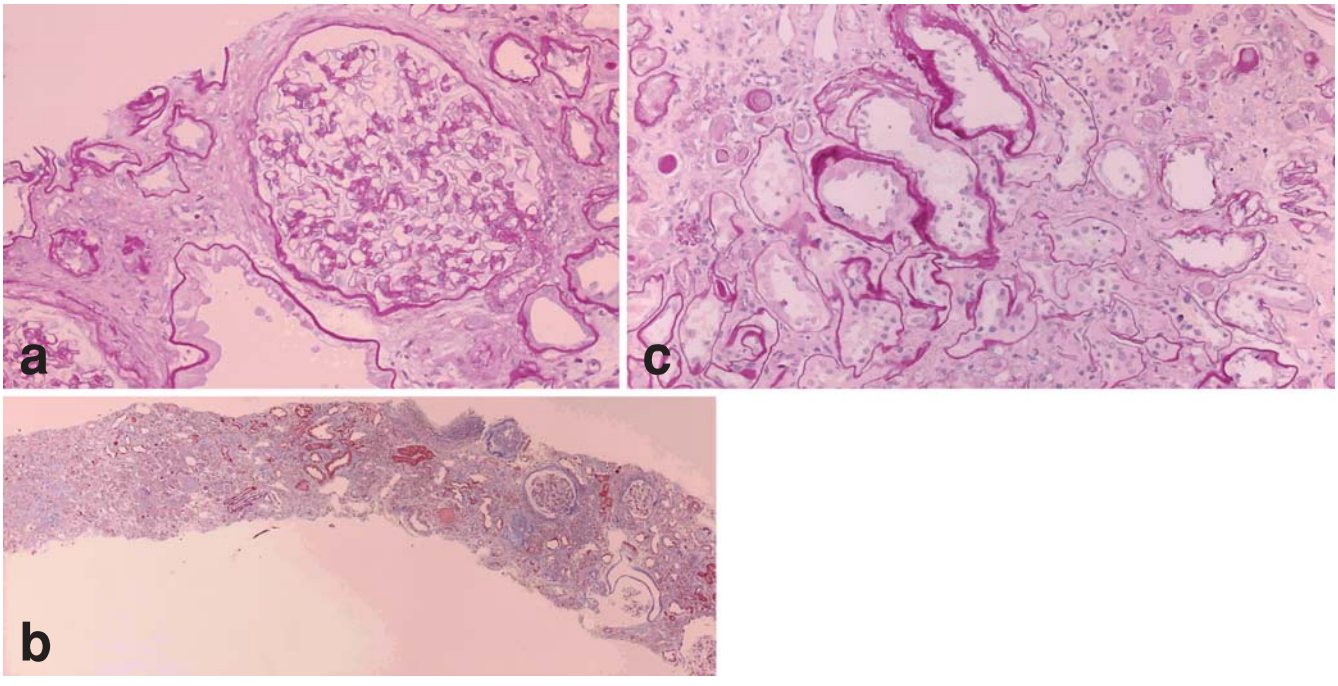

Fig. 4. **a** Light microscopic examination shows a mild increase in glomerular size but no mesangial cell proliferation (periodic acid-Schiff's reagent staining; ×20). **b,c** Marked atrophy and destruction of both proximal and distal tubules as well as interstitial fibrosis were observed, but cellular infiltration was scant (**b** Masson Trichrome staining, ×4; **c** periodic acid-Schiff's reagent staining, ×20)

exhibit features of secondary hyperparathyroidism, including increased numbers of osteoblasts and multinucleated osteoclasts with marrow fibrosis in the resorption surface. Cavities are apparent in severe cases. Our case associated with Fanconi syndrome similarly exhibited severe osteomalacia accompanied by secondary hyperparathyroidism.

Renal histologic findings typical for Fanconi syndrome include tubular atrophy with interstitial fibrosis, variable inflammation, and progressive glomerular sclerosis.[15] However, the intensity of inflammation cell infiltration in the tubulointerstitium is poorly characterized. In recent reports of Fanconi syndrome in patients with Chinese herb nephropathy,[16–20] renal histologic examination showed extensive tubulointerstitial fibrosis without glomerular lesions or cellular infiltration irrespective of progression or degree of renal injury. Our case also showed tubulointerstitial fibrosis with only scant inflammatory cell infiltration. Tubulointerstitial fibrosis has been considered to be a consequence of inflammatory cell infiltration into the area of the lesion. However, considering our case as well as those of Chinese herb nephropathy, the renal lesion of Fanconi syndrome may be tubulointerstitial fibrosis with scant cellular infiltrates and mild glomerular change. Chinese herb nephropathy is likely to involve a toxic substance such as aristolochic acid directly attacking the tubulointerstitium to induce fibrosis without cell infiltration. Since this histologic change also was present in our case of idiopathic Fanconi syndrome, severe acidosis, a factor common to both situations, may have caused tubulointerstitial fibrosis leading to renal insufficiency.

Osteomalacia associated with Fanconi syndrome has been thought to result from hypophosphatemia, low circulating 1,25-dihydroxyvitamin D, renal insufficiency, and chronic acidosis due to bicarbonate loss. Treatment including replacement of calcium, phosphate and vitamin D derivatives has been considered important.[10] However, in the present case, correction of acidosis only by administration of sodium bicarbonate gradually healed the bone disease, at which time parathyroid hormone increased rapidly. Calcitriol was effective in reversing this secondary hyperparathyroidism. Thus, adequate correction of acidosis as well as calcitriol replacement may be necessary in serious cases of osteomalacia associated with severe Fanconi syndrome.

In conclusion, symptomatic, histologically confirmed osteomalacia is rarely accompanied radiologically by typical Looser zones because of improvements in nutrition and medical practice. However, when Fanconi syndrome is accompanied by significant chronic acidosis, osteomalacia can cause severe skeletal complications but also can respond well to use of sodium bicarbonate.

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