Nontropical Sprue with Secondary Hyperparathyroidism

A Case Report and Review of the Literature

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NONTROPICAL SPRUE with its associated malabsorption of calcium and vitamin D (not to mention the defective absorption of foodstuffs, minerals, vitamins, and water) is one of the known causes of secondary hyperparathyroidism.[1–3] The following case of sprue is presented because of the extreme degree of the resultant osteitis fibrosa cystica.

CASE REPORT

Mrs. G. B. (U.M.H. 006454), a 54-year-old Caucasian, came to the Arthritis Clinic of The University of Michigan Medical Center in March 1962, with complaints of joint pains, limitation of motion, and generalized weakness of 53 years' duration.

She had been told that at age 2 she had "inflammatory rheumatism," and since then she had continued to have nonmigratory arthralgias not suggestive of inflammatory joint disease. She had never sustained fractures. In the past few years she had had continuous pain in her knees, hips, low back, and left thigh, and had been barely able to walk. Since age 19 she had lost 5 in. in height.

Concomitant with the childhood arthralgias, the diagnosis of "TB of the bowels" had been made on the basis of intractable diarrhea. The patient's physical development was retarded: she weighed only 18 lb. at age 3 and did not walk until age 5, at which time movement was awkward and accompanied by frequent leg pains and falling. From infancy to age 5 she had had almost continual "drawing-up" of her extremities, with the wrists, elbows, and knees held in flexion position. Menarche was at age 19, with menopause at age 41.

On admission the patient weighed 104 lb. She had lost 30 lb. in the past 25 yr. and had increasing difficulty in satisfying her hunger. She had persistently noted bulky, frothy, malodorous, floating, tan stools which adhered to the sides of the bowl, occurring 6–8 times a day, mostly nocturnally.

Anemia of 30 years' duration had been symptomatically treated with liver injections,

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folic acid, and vitamin B_{12} The patient had always been easily bruised, and after one episode, in 1961, of large spontaneous ecchymoses and rectal bleeding, she had received blood transfusions. At age 18 she had a large, beefy-red tongue, and massive edema with dyspnea, which required hospitalization. Additional past history indicated a bleeding peptic ulcer in 1936, and in 1937 a gallstone in the stool 2 weeks after the patient had suffered an attack of right-upper-quadrant abdominal pain.

Family history revealed that two of her sisters had developed slowly, and one of them has nontropical sprue. The patient's father had diabetes mellitus.

Physical examination revealed an edentulous, thin, and chronically-ill woman with marked wasting of muscle and subcutaneous tissue. Blood pressure was 100/70, with normal pulse and respirations. Heart and lungs were normal. Other findings included an obviously distended abdomen which showed visible small-bowel peristalsis and felt doughy. The organs were not palpable, and there was no ascites. Slight pretibial edema and mild varicosities were present in the legs. Bone and joint examination showed painful limitation of motion, most marked in the hips, knees, and ankles, with some bone pain in the thighs. There was no evidence of joint effusion or enlargement. A prominent dorsal kyphosis was present.

Admission urinalysis and hemogram were entirely normal. Stool guaiac was negative, as were the examinations for ova and parasites, and the cultures for stool pathogens. A glucose-tolerance test was performed: fasting, ½, 1, 1½, 2, 3, and 4 hr. samples being 73, 90, 126, 92, 75, 75, and 80 mg.%, respectively. Serum calcium ranged from 9.1 to 10.5 mg.%. Serum phosphate ranged from 1.4 to 2.2 mg.%. Serum alkaline phosphatase was initially 178 King-Armstrong units, but after initiation of treatment it dropped to 64 King-Armstrong units. Serum electrolyte values were sodium, 136 mEq./L.; potassium, 2.7 mEq./L. (which rose to 5.5 mEq./L. with administration of potassium triplex); chloride, 94 mEq./L.; and carbon dioxide, 27 mEq./L. Initial prothrombin concentration of 27% of normal (control, 11.5; and patient, 18.9 sec.) rose to 70% (12.7 sec.) after administration of oral vitamin K_1. Serum cholesterol was 140 mg.%, and total serum lipids were 825 mg.%, both of which are normal values in our laboratories. Total serum protein was 6.4 gm.%, with the electrophoresis showing 62.1% albumin, 5.9% α_1, 12% α_2, 11% β, and 9% γ globulin. Twenty-four-hour urine collection contained potassium, 22 mEq.; calcium, 87 mg.; phosphate 21.8 mg.; 17-ketosteroids, 4.7 mg.; and 17-hydroxysteroids, 3.2 mg. The Kahn, PBI, latex fixation, serum iron, serum acid phosphatase, BUN, and creatinine clearance were all normal or negative. Tubular reabsorption of phosphorus was 94.3% and 97.6% on a general diet, and 76% and 56% after addition of 1 L. of milk q.d. for 3 days.

A 24-hr. fecal volume was 1 L. (normal 100–200 ml.). Prior to therapy, while she was on a preparation diet containing 75–80 gm. fat and 100 gm. protein, 2 consecutive 6-day stool collections contained 53 gm. of fecal fat per day and 4.2 gm. fecal nitrogen per day.* Both of these values are abnormal, the normal fecal fat and nitrogen values being not over 5 gm. and 2 gm./24 hr., respectively.

Detailed radiologic examination of the small bowel showed marked absence of the normal mucosal pattern and striking puddling of barium, with increase in the transit time as seen in the accompanying 5-hr. film (Fig. 1). An unusually large caliber of the colon was noted on the barium enema. There was generalized skeletal demineraliza-

*Fecal fat determinations were carried out by the Gastrointestinal Research Laboratory of the University of Michigan Medical Center as a part of more extensive studies which will be reported elsewhere.

tion, and subperiosteal bone resorption was prominent in the phalanges (Fig. 2). Enlarged cystic lesions were noted in the long bones and bones of the hands. Most remarkable was the unusually large lytic lesion replacing several centimeters of the right fibula (Fig. 3). The calvarium showed a homogeneous, coarsely granular pattern, with

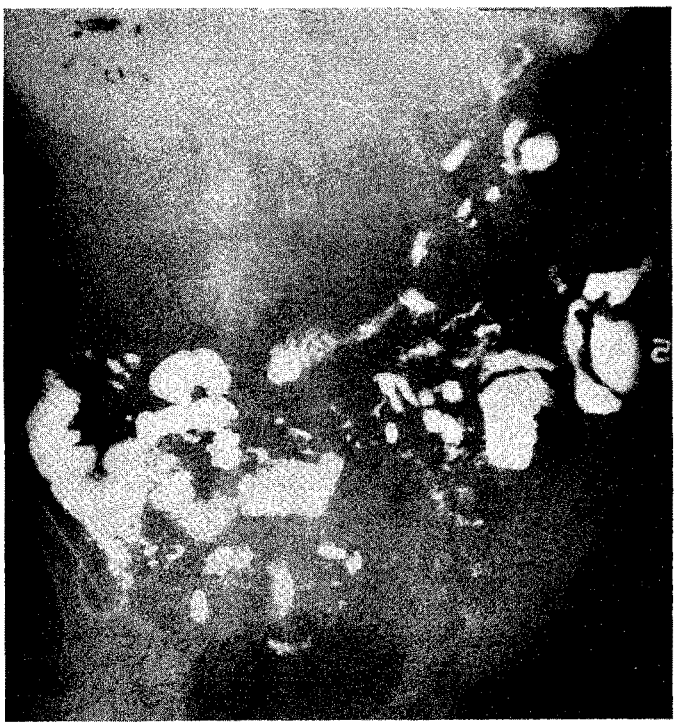

Fig. 1. Puddling of barium, variable lumen width, and striking delayed transit time, with no colonic fill, at 5 hr. during small-bowel study.

increased thickening of the bone (Fig. 4). The lateral chest film showed dorsal kyphosis, marked demineralization and mild "codfish" vertebral changes (Fig. 5). Oral cholecystogram revealed a faintly visible gallbladder without stones.

A small-bowel biopsy was performed in July 1962, using the multiple-retrieving small-bowel biopsy tube.[4] Macroscopically the specimen of jejunum showed typical changes of sprue, with flattened villi and visible crypts of Lieberkühn. Microscopic examination revealed atrophic villi which were broadened and blunted, and microvacuolar and degenerative changes in mucosal cells, with prominent round-cell (predominantly plasma-cell) infiltration of the lamina propria. All are representative of changes seen in nontropical sprue.

A gluten-free diet was instituted. In addition the patient was treated with potassium triplex; oral vitamin K_1, 20 mg. q.d.; calcium gluconate, 12 gm. q.d.; vitamin D, 75,000 U. q.i.d. initially and later reduced to 50,000 U. b.i.d. She was discharged from

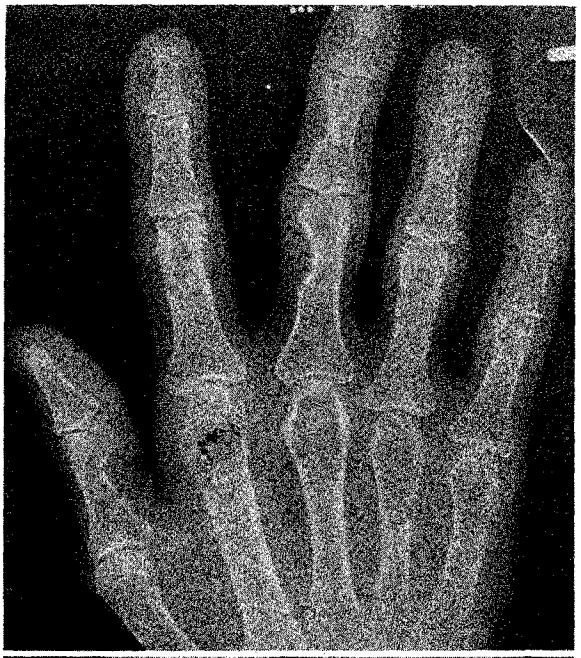

Fig. 2. Prominent subperiosteal bone resorption seen in phalanges.

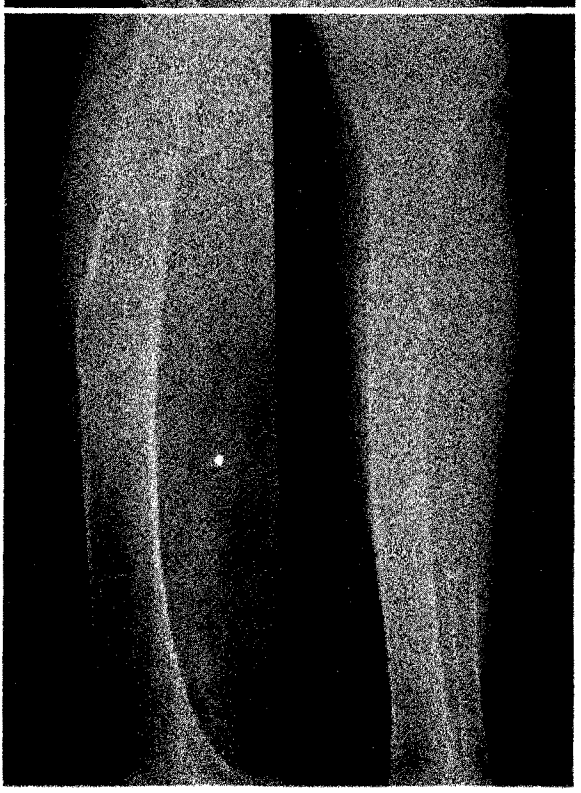

Fig. 3. Cortical thinning and trabecular cystic lesions of left femur (left), and large "brown tumor" replacing a portion of right fibula with periosteal elevation of distal fibula (right).

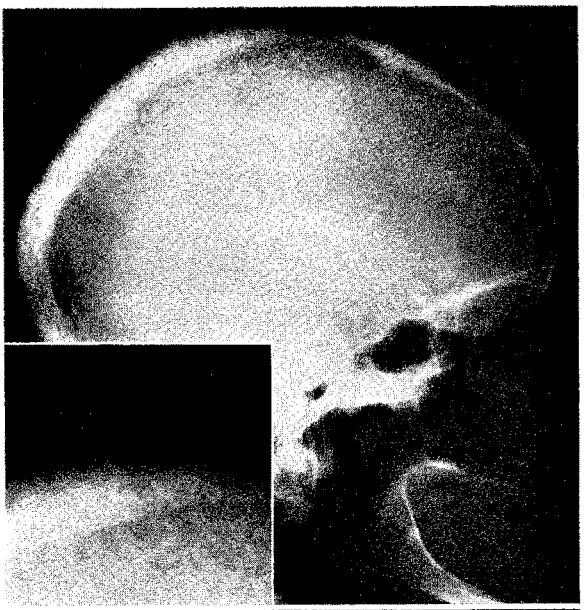

Fig. 4. Homogeneous coarsely granular pattern of calvarium, with increased bone thickness; typical changes of hyperparathyroidism. Insert is from section of vertex.

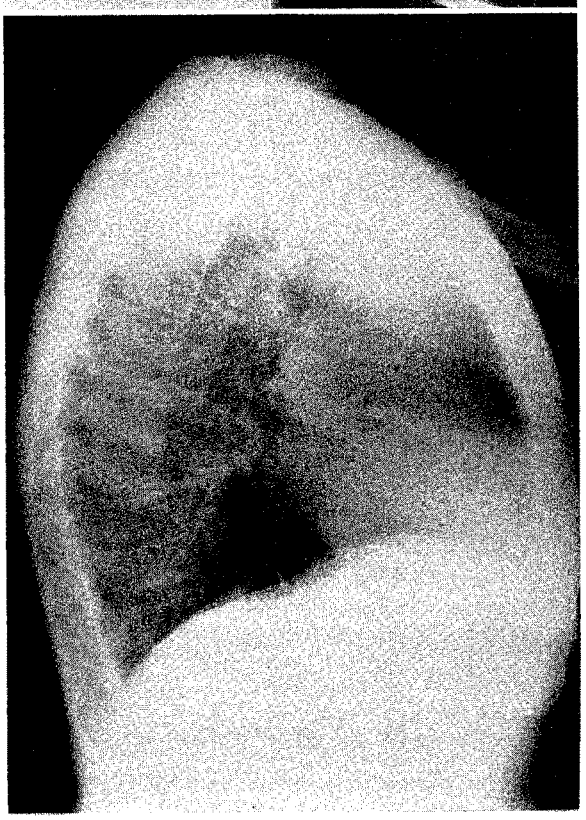

Fig. 5. Lateral view of chest demonstrates dorsal kyphosis, bone demineralization, and mild "codfish" vertebral changes.

the hospital in April 1962, on the gluten-free diet, vitamin D, and calcium-gluconate supplements.

By mid-May 1962, her 24-hr. fecal fat was 21 gm.* The patient has resumed her usual activities, walking with ease and without bone pain. Follow-up roentgenograms revealed rapid remineralization of the "brown tumor" in the right fibula and gradual improvement in the other osseous lesions. To date she shows symptomatic relief of her diarrhea, with one formed stool per day and a weight gain of 21 lb.; however, she continues to have abdominal distention and visible peristalsis.

COMMENT

This patient's lifelong illness illustrates nearly all the clinical facets of sprue. Whereas the incidence of sprue in the general population is 1:2000 to 1:4000, the incidence in the families of sprue patients is 1:50.[5] Her undiagnosed malabsorptive state in childhood (at least 30% of patients with sprue in some series had celiac disease) was mistaken for "TB of the bowel"—a frequently mentioned misdiagnosis in the older literature.[6] She had a typically late menarche and early menopause. Although growth was retarded, intestinal absorption was apparently adequate to protect her from deforming rickets (but inadequate to protect her from chronic tetany in childhood).

Various secondary manifestations of malabsorption, such as anemia, hypoprothrombinemia, diarrhea, and osseous and joint symptoms, were treated symptomatically through the years—in some respects successfully.

Her symptoms of pain, limited joint motion, and weakness finally brought her to our arthritis clinic. Initially, nontropical sprue and osteomalacia were suspected, but the roentgenologic finding of flagrant hyperparathyroid bone disease was not expected. The source of her left-thigh pain was the extensive cortical and medullary cystic disease, but surprisingly the large "brown tumor" of the right fibula was painless. In our literature review, 182 probable and proved cases of secondary hyperparathyroidism were found in sprue patients. We find that the bone disease of our patient is most extreme, and her serum alkaline phosphatase of 178 King-Armstrong units (higher than any of the reported cases) reflects the severity of her bone disease.

The normal serum-calcium and low serum-phosphate values are the result of the secondary hyperparathyroidism. The 24-hr. urinary-calcium excretion probably reflects the poor intestinal absorption and the bone depletion of calcium.

Of additional interest is the hypogammaglobulinemia in this patient which has previously been noted in patients with nontropical sprue.[7]

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DISCUSSION

Nontropical sprue was presumably first described by Aretaeus in the second century A.D., and in modern history by Samuel Gee in 1888.[8, 9] However, not until the 1950's was it suggested, on the basis of clinical observations by Dicke, that gluten might be an etiologic factor. Recent reviews extensively describe the current theories on this enteropathy.[5, 10, 11]

The first descriptions of symptomatic bone involvement in sprue appeared in the early twentieth century.[6, 12, 13] It was early recognized that malabsorption of ingested fat led to saponification with dietary calcium, with a resultant negative calcium balance.[6] Parsons observed that "coeliac rickets" was cured with ultraviolet light whereas renal rickets was not.[14] In 1927, it was pointed out that certain sprue patients with severe bony deformities and fractures had low serum-phosphate values; these cases responded to vitamin D administration.[15] Since that time it has been suggested that the hypophosphatemia frequently found in sprue is possibly caused by hypovitaminosis D with its ensuing hyperphosphaturia.[16] However, it has been otherwise stated that this phosphaturia is caused by hyperparathyroidism in response to hypocalcemia induced by malabsorption, especially of vitamin D and calcium.[17]

As early as 1926, parathyroid involvement in sprue was suggested on the basis of normal serum calcium levels even in cases with advanced bone changes.[18] Marble and Bauer determined in 1931 that the low serum calcium present in a case of sprue with bone changes, hypophosphatemia, and tetany did not represent hypoparathyroidism.[19] In 1932 Aub *et al.* stated that the hypophosphatemia in sprue was due to secondary hyperparathyroidism.[20] Since that time, various authors have added that secondary hyperparathyroidism in sprue is manifest by hypophosphatemia and either a low, or frequently a normal serum calcium, in addition to a spectrum of bone changes, from slight demineralization to fully developed osteitis fibrosa cystica.[21–23]

The signs and symptoms of osteomalacia in sprue are not unlike those found in osteomalacia of any cause or in primary hyperparathyroidism. Arthralgias, bone pain on local pressure, spontaneous fractures, and vertebral collapse, with obvious changes in stature and gait, are most common. Osteomalacia should be differentiated from osteoporosis, but in elderly sprue patients both entities may be present. The pain in extremities, bones, and joints in sprue may be both neurologic and osseous in origin and suggestive of arthritis, neuritis, fibrositis, or nucleus pulposus herniation.[24]

The earliest roentgenologic changes in bone may be pseudofractures; it is estimated that as much as 30–50% of bone calcium is gone before these linear bone lesions occur.[3, 24] "Pseudofracture" may be a misnomer,

since this is felt actually to represent a true partial fracture in demineralized bone exposed to excessive strain.[25] Other roentgenologic changes from rickets and/or osteomalacia to full-blown hyperparathyroid bone changes are demonstrated in various reports.[1, 6, 15, 24, 26] Striking cystic "brown tumors" of bone can be found in sprue patients with secondary hyperparathyroidism, but only one reported case compares with the extreme size of the osseous lesion demonstrated in our patient.[26]

The low serum calcium in malabsorption states is due to steatorrhea, hypovitaminosis D, and hypoproteinemia. An additional possible cause is excessive loss of endogenous calcium through digestive juices.[27–29] The parathyroid glands respond to the resultant hypocalcemia with hypersecretion of parathormone. However, the known effect of parathormone on increasing the mucosal absorption of calcium is absent in the face of malabsorption of vitamin D.

In 1906 Erdheim observed that osteomalacic patients had parathyroid hyperplasia.[17] As early as 1914 dietary experiments demonstrated the hyperplasia of the parathyroid glands resulting from calcium-poor diets.[17] If the glands are normally responsive, the increased release of parathormone has four basic mechanisms of action. Firstly, there is increased calcium reabsorption (↑Tm) in the renal tubule. Secondly, there is increased distal tubular secretion of phosphate. (Rasmussen and Reifenstein believe that this is a more likely renal action of parathormone than that of reducing the Tm for phosphate reabsorption).[17] Thirdly, there is increased resorption of calcium from bone. Fourthly, there is increased mucosal transport of calcium in the small intestine. Permissive amounts of vitamin D are required for all of these mechanisms to function. (Little is known of another effect of parathormone on the calcium and phosphate content of mammary gland secretions.) This action of the increased release of parathormone results in the return of calcium values toward normal, and in the sprue patient with chronic malabsorption of calcium, this causes eventual demineralization and osteomalacia with varying degrees of hyperparathyroid bone pathology. Whenever the solubility product ($[Ca^{++}] \times [PO_4^{\equiv}]$) falls below a critical level, as happens in sprue, there is a net movement of calcium ions from bone which, if chronic, leads to osteomalacia or rickets. Salvesen feels that osteomalacic bone disease in sprue is dependent to a large extent on the functional state of the parathyroids.[30]

Sprue patients with normal serum phosphate but low serum calcium are thought to have a state of relative parathyroid insufficiency. These patients lack osseous lesions of secondary hyperparathyroidism. Whether this is hypoparathyroidism or simply refractoriness to endogenous parathormone is not clear.[30, 31]

The incidence of secondary hyperparathyroidism in sprue is unknown. The reported cases certainly do not reflect the true incidence of this association. Of Salvesen's series of 85 cases, 40 had roentgenologic or chemical evidence of osteomalacia.[30] In another series of 94 sprue cases, 59.5% had osteomalacia, 28.3% had hypophosphatemia, and 61.5% had alkaline phosphatase elevation.[32] Of interest are the reports of documented osteomalacia and secondary hyperparathyroidism due to asymptomatic steatorrhea.[33, 34] The lower incidence of osteomalacia in sprue patients in the tropics has been noted, and it is theorized that the endogenous ergosterol formation increases their calcium absorption, protecting them from osteomalacia.[29, 32]

Treatment of the bone disease in sprue consists of concomitant administration of vitamin D, dietary calcium supplements, and the gluten-free diet.

The term "secondary hyperparathyroidism" is perhaps best known in the oft-reported cases of chronic renal insufficiency,[1, 14, 23, 35] but in 1954 Snapper *et al.* stated that, of various causes, malabsorptive states accounted for most cases of osteomalacia in New York state.[2] Besides sprue, other malabsorptive conditions such as biliary obstruction, pancreatic insufficiency, jejunoileitis, sclerodermatous involvement of the small bowel, gastrocolic fistula, gastroenterostomy, and extensive small-bowel resections are described as inciting secondary hyperparathyroidism.

SUMMARY

We have presented the case history of a patient with lifelong, classic nontropical sprue which was previously undiagnosed. She developed secondary hyperparathyroidism with extreme osteitis fibrosa cystica. As do some patients with malabsorption, she presented with musculoskeletal rather than gastrointestinal complaints.

Historical development of the etiology and pathophysiology of bone disease in sprue were reviewed.

Secondary hyperparathyroidism is believed to be a compensatory mechanism in response to the hypocalcemia of sprue.

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