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CASE REPORT

Acquired hypophosphatemia osteomalacia associated with Fanconi's syndrome in Sjögren's syndrome

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Abstract Sjögren's syndrome is an autoimmune disorder involving exocrine glands that occurs alone or in association with various autoimmune and connective tissue diseases. The severity of Sjögren's syndrome ranges from isolated sicca syndrome to severe complications such as vasculitis, lung and renal involvement. Overt or latent renal tubular acidosis caused by autoimmune tubulointerstitial nephritis, is a common extraglandular manifestation in Sjögren's syndrome. Osteomalacia is a rare complication of renal tubular acidosis, and it was reported to be associated with distal renal tubular acidosis in Sjögren's syndrome. We report a 60-year-old woman who presented with multiple bone deformity and general muscle weakness. Osteomalacia was secondary to Fanconi's syndrome, and the Fanconi's syndrome was a result of renal involvement in Sjögren's syndrome. Fanconi's syndrome is a rare kidney manifestation in Sjögren's syndrome. It may be latent and may precede the subjective sicca symptoms. These findings suggest that evidence for Sjögren's syndrome should be sought in adult patients with unexplained osteomalacia and renal tubular acidosis, even in the absence of subjective sicca syndrome. Conversely, in patients with Sjögren's syndrome, early investigation and treatment of renal tubular dysfunction may prevent future complications, such as osteomalacia.

Keywords Osteomalacia · Sjögren's syndrome · Fanconi's syndrome

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Introduction

Sjögren's syndrome (SS) is a connective tissue disorder affecting primarily the lacrimal and salivary glands, resulting in xerophtalmia and xerostomia. Non-exocrine organ systems may also be involved, including skin, lung, gastrointestinal tract, central and peripheral nervous system, muscular skeletal apparatus, and the kidney [1, 2]. Kidney involvement is a common extraglandular manifestation of SS [3]. Tubulointerstitial nephritis is usually revealed by a moderate decrease in renal function and, typically, by complete or incomplete distal renal tubular acidosis, a defect in distal acidification being reported in up to 33% of SS cases [4–6]. Proximal tubular defects and Fanconi's syndrome are less frequent. Signs of renal involvement, such as urine abnormalities and tubular defects, were most commonly identified in the absence of apparent clinical manifestations. Renal disease may precede the onset of the subjective sicca syndrome. Hypokalemic paralysis, nephritic syndrome, nephrogenic diabetes insipidus, distal tubular acidosis and urolithiasis, and osteomalacia due to renal tubular acidosis have been described as the chief manifestations of SS [7–12]. These findings make it clear that evidence for SS should be sought in adult patients with unexplained clinical and laboratory features. Even in the absence of

subjective sicca syndrome. We reported a 60-year-old woman who presented with multiple bone deformities and muscle weakness. She was later diagnosed to have osteomalacia secondary to Fanconi's syndrome. By further etiological investigation of acquired Fanconi's syndrome, SS was later revealed.

Case report

A 60-year-old woman presented with multiple bone deformities and generalized muscle weakness for months. The patient was a housewife. She reported that she had a minor car accident months ago, resulted in multiple bone fractures. Thereafter, deformities of the bone became prominent, followed by joint pains and gradually she became bedridden within a period of months. Days before this admission, generalized muscle weakness developed, followed by respiratory distress. She presented to our emergency room, where hypercapneic respiratory failure occurred requiring endotracheal intubation. She did not have nausea, vomiting, diarrhea or constipation, fevers, sweats, itching, or rash in the past several months. She did not smoke and reported no drug use.

Physical examination revealed a thin woman with multiple bony deformities, including thoracic and lumbar scoliosis, multiple rib fractures and bony protuberance and deformities of bilateral lower limbs due to previous fractures. The remainder of the physical examination showed no abnormalities. A skeletal X-ray showed a coarse trabecular pattern with severe demineralization in the femur, tibia, humerus and pelvis (Fig. 1). The whole body scan showed an increased tracer uptake at the sternum, multiple ribs, and bilateral shoulders (Fig. 2). The hemoglobin level was 10 g/dl, mean corpuscular volume 88 Fl, white-cell count 10,280/mm^3, platelet count 280,000/mm^3, levels of liver enzymes and the prothrombin time and partial-thromboplastin time were within normal ranges. The level of blood urea nitrogen was 28 mg/dl (6–22), serum creatinine 1.4 mg/dl (0.5–1.3), potassium 2.7 mmol/l (3.0–5.0), calcium 7.2 mg/dl (8.4–10.4), phosphorus 2.2 mg/dl (2.5–4.7), chloride 117 mmol/l (101–111), uric acid 2.5 mg/dl (2.1–7.1), alkaline phosphatase 256 IU/l (43–122), and albumin 3.5 mg/dl (3.5–5.1). The fasting plasma glucose was 112 mg/dl (60–110). The blood pH was 7.2 (7.38–7.44), the partial pressure of carbon dioxide 21 mmHg (35–45), and the bicarbonate level 8.2 mEq/l (21–30). The calculated anion gap was 11.8 meq/l (12 ± 2). The urinary pH was 8.5 (5.0–9.0); the daily urine output was 1,770 ml; the potassium level was 13 mmol/l (25–100); calcium 96 mg/day (<300); and

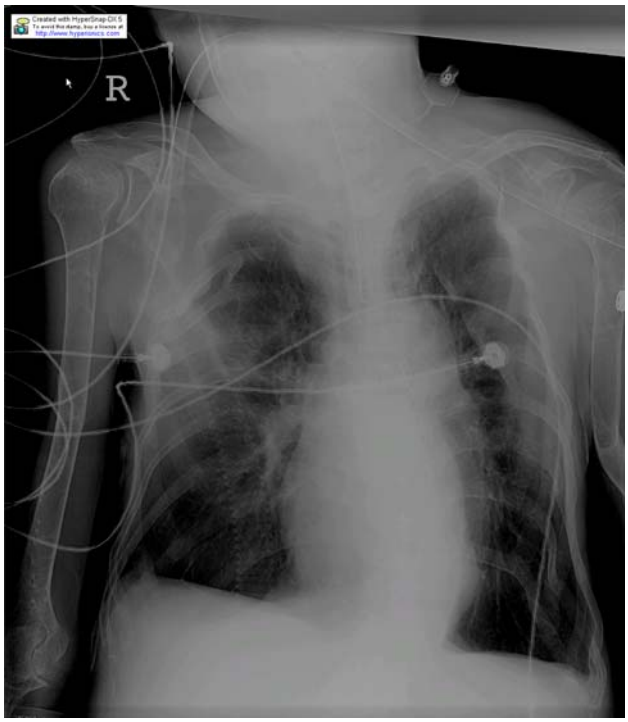

Fig. 1 Chest X-ray showing severe bony deformities of rib cage, bilateral humeral shaft fractures and marked cortical bone thinning

phosphate 478 mg/day (400–1,300). The urinary anion gap was 33 (−10 to +10). The fractional excretion of phosphate was 41 (5–20%). Persistent glycosuria was found associated with normal plasma glucose level. Serum parathyroid hormone level was 130 pg/dl (11–62), 25-dihydroxyvitamin D 11.4 pg/ml (9.7–14.7), and 1,25-dihydroxyviatamin D 33 pg/ml (15.9–55). The serum ceruloplasmin, mercury and lead level were normal. Thyroid function was normal. There was generalized aminoaciduria (Table 1). The antinuclear antibody and anti-Ro were positive. Rheumatic factor and immunoglobulin titers were normal. Schirmer test was abnormal and lip biopsy showed multiple mononuclear cells infiltration over periductal area (Fig. 3). She was then treated with phosphate and vitamin D3.

Discussion

The present case of SS was a difficult diagnostic challenge due to its uncommon presentation. The main presentation of our patient was the bone deformity and muscle weakness. Our patient's clinical feature may be due to hypophosphatemia. Although the bone biopsy was not performed, hypophosphatemic osteomalacia was suggested by the biochemical profile: hypophosphatemia, hyperphosphaturia with reduction of the tubular reabsorption of phosphate, normal calcium

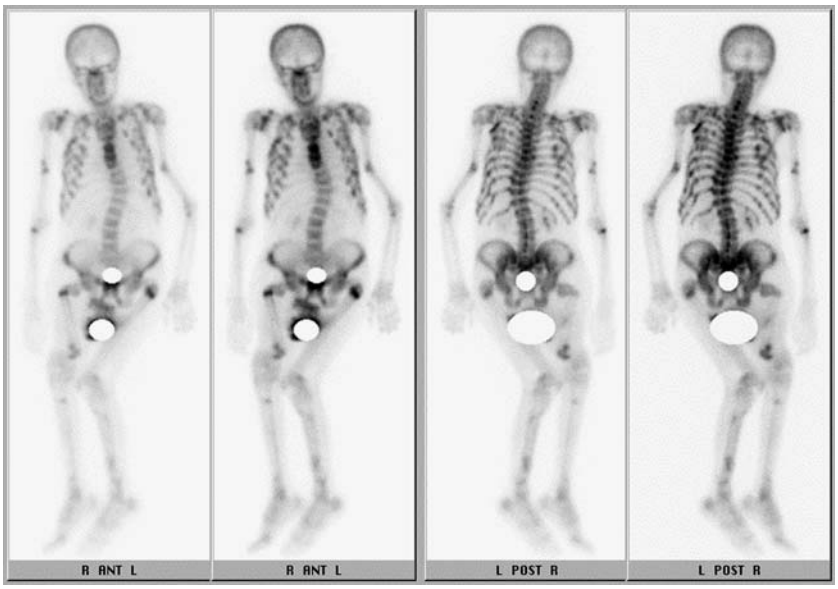

Fig. 2 Bone scan image showing multiple hot spots over the rib cage and extremities. There are multiple non-union fractures on the long bones. Cervical and thoracic spine scoliosis is also noted

Table 1 Analysis of 24-h urine protein for amino acid by HPLC method

Component	Retention time	Peak area	Response factor	Concentration μmol/g of Cre	Reference range in μmol/g of Cre
Taurine	2.77	254.46259	6.72248	2421.11	90–1,049
Aspartic acid	11.23	19.02446	6.30707	169.82	20–44
Hydroxyproline	12.14	287.76834	169.23219	68926.62	0–60
Threonine	14.43	870.97968	6.10532	7526.23	40–232
Glutamic acid	18.59	239.55872	5.31087	1800.69	0–28
Glutamine	20.24	1570.59436	12.81278	28481.87	96–604
α-aminocadipic	24.56	18.44835	8.01848	209.37	0–56
Proline	28.63	28.17783	198.85942	7930.76	0
Glycine	30.18	1264.03125	5.45934	9766.95	275–3,378
Alanine	32.37	1297.05090	6.04887	11104.33	66–366
Citrulline	33.70	350.08899	6.79527	3367.02	0–12
α-aminobutyric	35.40	7.44959	4.03065	42.50	0–31
Valine	36.30	780.51208	6.24046	6893.78	0–72
Methionine	38.70	53.02853	5.63880	423.21	16–108
Isoleucine	42.40	163.60298	6.10937	1414.65	12–36
Leucine	43.76	312.24374	5.88059	2598.82	8–82
Tyrosine	46.32	414.70505	6.29018	3692.01	24–152
Phenylalanine	51.76	254.88398	5.80855	2456.17	4–88
Ornithine	98.89	127.64305	5.25406	949.19	0–56
Lysine	102.61	1116.03845	5.20260	8217.90	17–148
Carnosine	119.21	10.29957	17.85393	260.26	0–20
Arginine	127.91	84.20676	6.25374	745.33	8–52

metabolism, normal 25-dihydroxyvitamin D and inappropriate normal 1,25-dihydroxyvitamin D and secondary hyperparathyroidism in front of a low serum phosphorus level; as well as thinning of the trabeculae and the cortex with loss of bone density in the radiologic study.

A number of different disorders are associated with osteomalacia. The leading causes are nutritional and intestinal diseases. Acquired hypophosphatemia osteomalacia has been reported as a complication of multiple myeloma, monoclonal gammopathy of undetermined significance, and lymphocytic lymphoma [13, 14].

Osteomalacia rarely occurs in a connective tissue disease such as SS [12, 15–18]. When it occurs, it may be a result of kidney involvement, including tubulointerstitial nephritis and tubular dysfunction. In the review of the literature, five cases have been reported with osteomalacia as the first manifestation of SS. In all of these cases, the osteomalacia was related to distal renal tubular acidosis, except one reported to be a

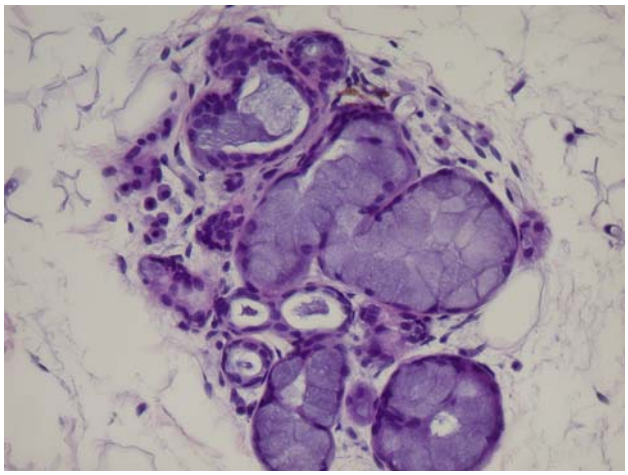

Fig. 3 Histology of lip biopsy, H&E stain, 400×. Numerous mononuclear cells infiltration over the glandular structure of lip was found, compatible with Sjögren's syndrome

mixed distal and proximal renal tubular acidosis (Table 2). The explanation for the osteomalacia that occurs in distal renal tubular acidosis is the combination of acidosis and hypophosphatemia, and coexisting vitamin D deficiency may be an aggravating factor [19]. In contrast to these cases, the osteomalacia of our patient was related to Fanconi's syndrome, although there were also some components of distal renal tubular acidosis.

Little is known about proximal tubular dysfunction in SS. To our knowledge, only eight case-reports of Fanconi's syndrome in primary SS have been published to date [6, 9, 20–23]. It may be complete including proximal tubular acidosis or incomplete with the absence of glucosuria and intact $TmHCO_3$. Contrasting with the usual preservation of distal tubular function in adult Fanconi's syndrome, it may exhibit at least one distal tubular abnormality when it is associated with SS. Although the bicarbonate loading test was not done in our patient, the diffuse aminoaciduria and normoglycemic glucosuria favored the complete form of Fanconi's syndrome. As previous reports, our patient also showed characteristic of distal tubular dysfunction, such as alkalized urine.

Table 2 The main renal tubular dysfunction characteristics of patients manifested with osteomalacia in primary Sjögren's syndrome in the review of literature

First author	Age	Gender	Clinical presentation	Type of RTA
Pal et al.	52	F	Hip and back pain	Distal
Neto et al.	41	F	Osteoarticular pain and muscle weakness	Distal [a]
Hassouri et al.	40	F	Generalized bone pain	Distal
Okazaki et al.	43	F	Bone pain and pseudofracture	Distal
Okada et al.	53	F	General bone pain	Distal
Our patient	60	F	General bone pain and muscle weakness	Fanconi's syndrome

[a] Proximal tubular dysfunction was noted by urinary excretion of β-2-microglobulin

Although Fanconi's syndrome is a well-known cause of osteomalacia, previous reports of Fanconi's syndrome in SS did not describe the occurrence of osteomalacia. The duration and severity of the phosphate leak correlates well with development of osteomalacia and therefore probably may explain the osteomalacia in our patient.

We believed that the tubular dysfunction of our patient was long-standing without overt manifestation until the bone deformity supervenes.

In conclusion, the kidney involvement in SS may be latent and may precede the typical sicca symptoms, therefore, autoimmune investigations for SS should be investigated in any patient presenting with osteomalacia from renal tubular dysfunction, even in the absence of subjective sicca syndrome. In addition, in patients with SS, early investigation and treatment of renal tubular dysfunction may prevent future complications, such as osteomalacia.

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