Osteomalacia secondary to renal tubular acidosis due to Sjögren's syndrome: a case report and review of the literature

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Abstract A 43-year-old woman was admitted to our hospital because of generalized bone pain. Arterial blood gas showed pH 7.266, HCO_3^- 13.5 mEq/l, and anion gap (AG) 12. Since her urine pH was 7.0 despite metabolic acidosis with normal AG, we diagnosed distal renal tubular acidosis (RTA). Serum phosphate was 2.5 mg/dl, the level of β_2 microglobulin was 41100 $\mu\text{g/l}$, and aminoaciduria was present. These results indicated proximal tubular dysfunction. The radiograph showed pseudofracture in the pubic bone, indicating osteomalacia. Bone scintigram showed abnormal accumulations of $^{99\text{m}}\text{Tc}$ -HMDP in multiple joints. Then, her generalized bone pain was considered to be a symptom of osteomalacia. Despite the absence of overt Sicca syndrome, the evaluation of Sjögren's syndrome (SjS) as a cause of distal RTA was performed. Antibodies to the SS-A level was 127U/ml. Tear break-up time was 3 s bilaterally and salivary gland scintigraphy showed low uptake of $^{99\text{m}}\text{Tc}$ in the submandibular glands and the parotids. Thus, we diagnosed SjS finally. Gallium scintigraphy showed mild abnormal uptake in bilateral kidneys, suggesting acute tubulointerstitial nephritis. After treatment with prednisolone, alfacalcidol, and sodium bicarbonate, bone pain was remarkably relieved. Additionally, aminoaciduria disappeared and the level of β_2 microglobulin decreased. We speculated that the coincidence of proximal tubular dysfunction and distal RTA cause a severe manifestation of osteomalacia.

Keywords Osteomalacia · Renal tubular acidosis · Sjögren's syndrome

Introduction

Sjögren's syndrome (SjS) is a chronic inflammatory disorder affecting lacrimal and salivary gland function. It is a systemic disease, with manifestations from several organ systems, such as lung, skin, gastrointestinal tract, central and peripheral nervous system, muscles, and the kidney [1]. Renal involvement, such as tubulointerstitial nephritis, renal tubular acidosis (RTA), and glomerular disease, may occur as an extraglandular manifestation of SjS [2]. Although RTA is one of the causes of osteomalacia [3], only a few case reports of osteomalacia with SjS have been published. Here, we report a case diagnosed as osteomalacia associated with SjS and reviewed the literature.

Case report

A 43-year-old woman was admitted to our hospital in August 2010 because of generalized bone pain. She had developed right chest pain and back pain, without antecedents, at age 42 years. At that time, she was diagnosed as right rib fracture and vertebral fracture, and was administered non-steroidal anti-inflammatory drugs. Thereafter, her symptoms worsened and she had developed left ankle pain. No other family members had osteomalacia or bone metabolic diseases. She had no history of malabsorption, short stature, or limb deformity. She had been taking no drugs or metals that might have caused RTA or osteomalacia.

Her height, body weight, and body mass index were 150 cm, 43.0 kg, and 19.1 kg/m^2 , respectively. Her blood

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pressure was 118/64 mmHg, pulse rate was 76 beats/min, and body temperature was 36.6. Physical examination was not remarkable except for the pain in her ribs, back, and left ankle.

Complete blood count showed white blood cell count $4.3 \times 10^3/\mu\text{l}$ ($4.3 \times 10^9/\text{l}$) and hemoglobin 14.1 g/dl (141 g/l). Blood chemistry showed blood urea nitrogen 14.2 mg/dl (5.1 mmol/l), creatinine 0.8 mg/dl (70.7 $\mu\text{mol/l}$), sodium 143 mEq/l (143 mmol/l), potassium 2.8 mEq/l (2.8 mmol/l), chloride 117 mEq/l (117 mmol/l), calcium 9.3 mg/dl (2.3 mmol/l), phosphate 2.5 mg/dl (0.8 mmol/l), uric acid 2.9 mg/dl (172.5 $\mu\text{mol/l}$), albumin 4.2 g/dl (42 g/l), and alkaline phosphatase (ALP) 897 U/l: ALP2 29 %, ALP3 71 %. Arterial blood gas showed pH 7.266, pO_2 116 mmHg, PCO_2 30 mmHg, HCO_3^- 13.5 mEq/l (13.5 mmol/l), and anion gap (AG) 12 mEq/l (12 mmol/l). Urinalysis showed pH 7.0, no proteinuria, no hematuria, and no glycosuria, and the urinary sediment was not significant. A diagnosis of distal RTA was made because her urine showed alkalinity, despite severe metabolic acidosis with normal AG. The level of urinary excretion of $\beta 2$ microglobulin was 41100 $\mu\text{g/l}$ and aminoaciduria was present. The percentage of tubular reabsorption of phosphate (%TRP) was 70 %. Therefore, proximal tubular dysfunction was evident. Serum intact parathyroid hormone level was 25.6 pg/ml (25.6 ng/l, normal 10–65 pg/ml), 25-dihydroxyvitamin D was 11.6 ng/ml (29.0 nmol/l, normal 9.0–33.9 ng/ml), and 1,25-dihydroxyvitamin D was 15 pg/ml (39 pmol/l, normal 20–60 pg/ml). There was bilateral nephrocalcinosis on plain abdominal radiography,

abdominal echography, and computed tomography. The radiograph of the pelvis showed pseudofracture, i.e., Looser's zone, in the pubic bone, which indicated osteomalacia (Fig. 1). Bone scintigram showed abnormal accumulations of $^{99\text{m}}\text{Tc}$ -HMDP in the left clavicle, bilateral ribs, L4 spine, pelvis, and left ankle. After examinations of whole-body computed tomography, gastrointestinal endoscopy, colonoscopy, and mammography, bone metastases of malignancy were excluded. Gallium (Ga) scintigraphy showed mild abnormal uptake in bilateral kidneys, left articulation sternoclavicularis, left inguinal lesion, and left ankle. The uptake of Ga-citrate in the kidney suggested tubulointerstitial nephritis (Fig. 2). A test of antinuclear antibodies was positive in a titer of 1:160 with a speckled pattern; the level of antibodies to SS-A was 127 U/ml (normal 0–30 U/ml) and SS-B was negative. Tear break-up time was 3 s bilaterally. Salivary gland scintigraphy revealed low uptake in the submandibular glands and the parotids. According to the clinical findings and laboratory data, she was diagnosed as osteomalacia and SjS.

The clinical course is shown in Fig. 3. The administration of 0.25 μg alfacalcidol and 3 g sodium bicarbonate was started, in order to treat osteomalacia. One month later, serum phosphate elevated to 3.7 mg/dl. However, generalized bone pain diminished partially. Six months later, 30 mg prednisolone was additionally administered. Her symptom promptly ameliorated thereafter. Seven months after treatment, serum ALP was normalized and 1 year after treatment, aminoaciduria disappeared. %TRP also improved to 84 %.

Fig. 1 Radiograph of the pelvis. The arrows show pseudofracture in the pubic bone

Discussion

We reported a case of osteomalacia secondary to distal RTA due to SjS. In our case, the existence of distal RTA was definite because of constant high urine pH in spite of severe acidemia. Nephrocalcinosis was compatible with distal RTA. Since the patient's main symptom was generalized bone pain rather than Sicca syndrome, it was very difficult to make a diagnosis of SjS. It took about 1 month to make the final diagnosis of SjS.

Osteomalacia has been rarely reported in SjS patients. Since the first report [14] of the case of SjS with osteomalacia was published in 1977, as far as we investigated, only 13 cases have been reported in English and Japanese so far [4–16]. Previous published case reports are summarized in Table 1. The median age was 41 years, ranging

Fig. 2 Gallium scintigraphy. Mild uptake of Ga-citrate was observed in bilateral kidneys (arrow), left articulation sternoclavicularis, left inguinal lesion, and left ankle

from 30 to 71 years, and all cases were women. Osteomalacia was the first manifestation of SjS in seven cases. All cases of osteomalacia with SjS developed distal RTA and two patients developed mixed distal and proximal RTA [11, 16], confirmed by the sodium bicarbonate loading test. The other eight patients [4, 6–10, 12, 13] showed evidence of proximal tubular dysfunction, such as aminoaciduria, renal glycosuria, hypophosphatemia, hypouricemia, or a high level of urinary excretion of $\beta 2$ microglobulin.

Distal RTA is characterized by impaired distal acid secretory capacity. This defect leads to an inability to excrete the daily acid load, resulting in progressive hydrogen ion retention and a decrease in plasma bicarbonate concentration. The diagnosis of distal RTA is made by the presence of alkaline urine under metabolic acidosis with normal AG. Causes of distal RTA in adults include hypercalciuria and autoimmune diseases, such as SjS and rheumatoid arthritis [17]. Although distal RTA is reported to occur in 11–30 % of patients with SjS [2, 18], the mechanism of distal RTA in SjS is not fully understood. Since urinary acidification in the collecting tubules is achieved via H^+ secretion by a luminal H^+ -ATPase pump, diminished H^+ -ATPase activity is thought to be one of the causes of distal RTA [19]. Cohen et al. [20] reported that an absence of H^+ -ATPase in the cortical collecting tubules was observed in the kidney biopsy specimen of a patient with distal RTA with SjS. Fulop and Mackay [12] documented that there seemed to be no better explanation for the bone disease in SjS than some combination of acidosis and hypophosphatemia. Coexisting vitamin D deficiency, when present, may be an aggravating factor. In our case, metabolic acidosis, hypophosphatemia, and vitamin D deficiency existed. Thus, osteomalacia in our

Fig. 3 Clinical course. Administration of alfacalcidol and sodium bicarbonate were started in order to treat osteomalacia and 6 months after prednisolone was added. Bone pain ameliorated and serum alkaline phosphatase (ALP) normalized

Table 1 Summary of the published literature of cases with osteomalacia in Sjögren's syndrome (SjS)

References	Age (years)	Sex	Osteal manifestation	SS	Serum levels					Cr (mg/dl)	IP (mg/dl)	ALP (IU/l)	25(OH)D (ng/ml)	1,25(OH)D (pg/ml)	PTH
					Blood pH	K (mEq/l)	K (mEq/l)	IP (mg/dl)	Cr (mg/dl)						
Our case	43	F	Chest pain, back pain, left ankle pain	–	7.26	2.8	2.5	2.5	0.8	897	→	→	↓	→	→
[4]	60	F	Bone deformities	–	7.2	2.7	2.2	2.2	1.4	256	→	→	→	→	↑
[5]	71	F	Vertebral collapse, hip fracture	+	7.21	3.2	NA	NA	2.9	NA	NA	NA	NA	NA	NA
[6]	40	F	Bone and joint pain	+	NA	3.5	2.3	2.3	1.6	210	NA	NA	NA	NA	NA
[7]	39	F	None	+	7.277	2.6	1.8	1.8	1.3	106	NA	NA	NA	NA	↑
[8]	53	F	Overall aches	+	7.21	2.9	2.4	2.4	0.8	1302	NA	NA	NA	NA	↑
[9]	41	F	Osteoarticular pain	+	7.19	2.8	2.3	2.3	NA	205	NA	NA	NA	NA	→
[10]	42	F	Chest pain	+	7.347	3.7	2.4	2.4	1	190	→	→	→	→	↑
[11]	30	F	Back pain, leg pain	+	7.34	4.8	3.6	3.6	4.8	372	→	→	→	→	→
[12]	38	F	General body aches	+	7.18	3	1.7	1.7	0.8	351	↓	→	→	→	→
[13]	34	F	Bone pain	–	NA	NA	2.2	2.2	NA	322	→	→	NA	NA	→
[14]	64	F	Leg pain	+	7.27	2.6	→	→	1.3	↑	NA	NA	NA	NA	NA
[15]	52	F	Hip and back pain	+	NA	NA	2.8	2.8	0.9	139	→	→	NA	NA	NA
[16]	37	F	Left leg pain, rib pain	+	7.28	3.2	1	1	1.3	↑	NA	NA	NA	NA	→

References	Age (years)	Sex	Osteal manifestation	dRTA	Proximal tubular dysfunction				Treatment			
					AA	RG	IP↓	UA↓	BMG↑	CS	Vit. D	Alkali therapy
Our case	43	F	Chest pain, back pain, left ankle pain	+	+	–	+	–	+	+	+	+
[4]	60	F	Bone deformities	+	+	+	+	–	NA	+	+	+
[5]	71	F	Vertebral collapse, hip fracture	+	–	–	NA	NA	NA	+	+	+
[6]	40	F	Bone and joint pain	+	NA	NA	+	NA	NA	+	+	+
[7]	39	F	None	+	NA	NA	+	NA	NA	+	+	+
[8]	53	F	Overall aches	+	NA	NA	+	NA	+	+	+	+
[9]	41	F	Osteoarticular pain	+	NA	NA	+	NA	+	+	+	+
[10]	42	F	Chest pain	+	–	–	+	+	+	+	+	+
[11]	30	F	Back pain, leg pain	+	+	+	–	–	NA	+	+	+
[12]	38	F	General body aches	+	NA	NA	+	NA	NA	+	+	+
[13]	34	F	Bone pain	+	NA	–	+	NA	NA	+	+	+
[14]	64	F	Leg pain	+	–	–	–	NA	NA	+	+	+
[15]	52	F	Hip and back pain	+	–	NA	NA	NA	NA	+	+	+
[16]	37	F	Left leg pain, rib pain	+	+	–	+	+	+	+	+	+

Conversion factors for units: serum IP in mg/dl to mmol/l, $\times 0.3229$; serum Cr in mg/dl to mol/l, $\times 88.4$; serum 25(OH)D in ng/ml to nmol/l, $\times 2.496$; serum 1,25(OH)D in pg/ml to pmol/l, $\times 2.6$. No conversion necessary for serum K in mEq/l and mmol/l

→ normal, ↑ elevated, ↓ decreased, NA not available, SS Sjögren's syndrome, K potassium, IP phosphate, ALP alkaline phosphatase, 25(OH)D 25-dihydroxyvitamin D, 1,25(OH)D 1,25-dihydroxyvitamin D, PTH parathyroid hormone, dRTA distal RTA, AA aminoaciduria, RG renal glycosuria, IP↓ hypophosphatemia, UA↓ hypouricemia, BMG↑ high level of urinary excretion of β_2 microglobulin, CS corticosteroid, Vit. D vitamin D, Ca calcium supplement

case might be explained by distal RTA alone. However, if so, why were there only 13 cases that developed osteomalacia associated with SjS?

Proximal RTA is a well-known cause of osteomalacia [3]. This fact may be due, in part, to phosphate wasting and subsequent hypophosphatemia and to acquired vitamin D deficiency, since the proximal tubule is a major site of formation of activated vitamin D. Additionally, acidemia can directly decrease in bone mineralization. The causes of proximal RTA in adults include multiple myeloma, hypocalcemia, drugs, heavy metals, amyloidosis, renal transplant rejection, or SjS [19]. As mentioned above, 10 out of 13 cases of osteomalacia with SjS developed proximal tubular dysfunction or proximal RTA in addition to distal RTA. We speculated that the aggravation of decrease in bone mineralization due to proximal tubular dysfunction, as well as distal RTA, seemed to cause a severe manifestation of osteomalacia in our case.

Tubulointerstitial nephritis might be a causative factor for RTA in SjS. In the review of the literature, renal biopsy was performed for five out of 13 cases and all biopsy specimens showed tubulointerstitial nephritis. We tried to perform renal biopsy in this patient. However, this was not possible because of severe generalized bone pain. She could not even lie on her stomach. Ga-citrate uptake in both kidneys was compatible with tubulointerstitial nephritis. At first, we administrated alfacalcidol and sodium bicarbonate, but its effect on bone pain was limited. Thus, we decided to use prednisolone for the treatment of underlying SjS. After the administration of prednisolone, the bone pain almost completely disappeared. We speculated that prednisolone ameliorated tubulointerstitial nephritis in SjS, resulting in improvement of tubular function. In fact, laboratory abnormalities indicating proximal tubular dysfunction such as aminoaciduria, hypophosphatemia, and high level of urinary excretion of β_2 microglobulin improved and, concurrently, bone pain relieved.

We report a case of osteomalacia secondary to distal RTA due to SjS. Even in the absence of overt Sicca syndrome, SjS should be considered as one of the causal diseases in the patient presenting generalized bone pain.

Conflict of interest None.

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