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Case report:

CHONDROCALCINOSIS AND OSTEOPOROSIS IN A PATIENT WITH RENAL TUBULAR DISORDER

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ABSTRACT

We report the case of a 50-year old male patient presenting with a combination of chondrocalcinosis and osteoporosis related to a renal tubular disorder. Laboratory studies revealed hypokalemia, hypomagnesemia, hypocalcemia with renal wastage and metabolic alkalosis, compatible with a renal tubular transport disorder with similarities to Bartter's and Gitelman's syndrome. Calcifications of the menisci and cartilage on X-rays of knee joints suggested chondrocalcinosis, which has been associated with Gitelman's syndrome. Radiologically suspected osteopenia was confirmed by a bone density scan that revealed osteoporosis of the vertebral column. An association of osteoporosis with hypercalciuria, which commonly occurs in Bartter's syndrome patients, has been reported. Upon treatment of the renal tubular disorder with spironolactone and a thiazide diuretic in combination with calcium and magnesium supplementation, the electrolyte abnormalities resolved and arthralgias disappeared. Our case demonstrates a renal tubular dysfunction with features of both Bartter's and Gitelman's syndrome along with concurrent chondrocalcinosis and osteoporosis. Furthermore, the occurrence of osteoporosis in this relatively young patient, in the absence of other risk factors, demonstrates that renal tubular disorders should be suspected in presenile osteoporosis. Vice versa, since osteoporosis usually is asymptomatic before fracturing, patients with renal tubular disorders should be examined for osteoporosis.

Keywords: Osteoporosis, chondrocalcinosis, hypocalcemia, Bartter's syndrome, Gitelman's syndrome

CASE REPORT

The male patient first presented at the age of 49, with arthralgias of hands, feet and shoulders, early morning stiffness and leg cramps. Weakness in the right hand was attributed to a carpal tunnel syndrome. The patient had a daily intake of two glasses of wine, no history of vomiting, and he was taking no medications with the exception of diclofenac in a dose of 100 mg/d. At the age of twenty he suffered a traumatic fracture of his left hip, which was treated with a total endoprosthesis.

Physical examination revealed the patient to be afebrile with a blood pressure of 130/90 mmHg and a heart rate of 87/min. He was overweight with a body mass index of 32. No synovialitis was detectable on physical examination. Gaenslen's sign was positive on the left foot. Physical examination of heart, lungs, and abdomen was normal.

Neurological examination displayed muscular weakness in the right hand but no sensory deficit.

Blood tests revealed hypokalemia, hypomagnesemia, hypocalcemia, while serum levels of sodium and phosphate were normal. Urinary potassium, magnesium and calcium were high in face of their low serum concentrations (summarised in Table 1), consistent with renal wasting. Blood gas analysis revealed metabolic alkalosis. A complete blood count and coagulation tests showed no abnormalities. Values for serum protein concentration, liver enzymes, alkaline phosphatase, and for 1,25 $(OH)_2$ vitamin D were normal, while intact parathyroid hormone (PTH) was elevated. Plasma aldosterone levels and urine aldosterone-18-glucuronide metabolites were increased. Both serum creatinine and creatinine clearance were normal, indicating normal glomerular filtration. Slightly elevated titers of antinuclear antibodies (ANA) were found, while titers of extractable nuclear antibodies, anti-neutrophilic cytoplasmic antibodies, and rheumatoid factor were negative. Serum levels of telopeptides (ICTP) were increased, whereas osteocalcin was normal. Finally, the ratio of urinary deoxypyridinoline to creatinine was increased, indicating bone resorption.

Radiographic analysis showed articular and periarticular calcifications in the shoulders, knees, and feet consistent with chondrocalcinosis (**Fig. 1**). Moreover, osteopenia was demonstrated in the lumbar spine without signs of fractures. Bone density scan revealed osteopenia with a T-score value of –2.0 in the Ward's triangle of the femur and osteoporosis with a value of –2.7 in the lumbar spine.

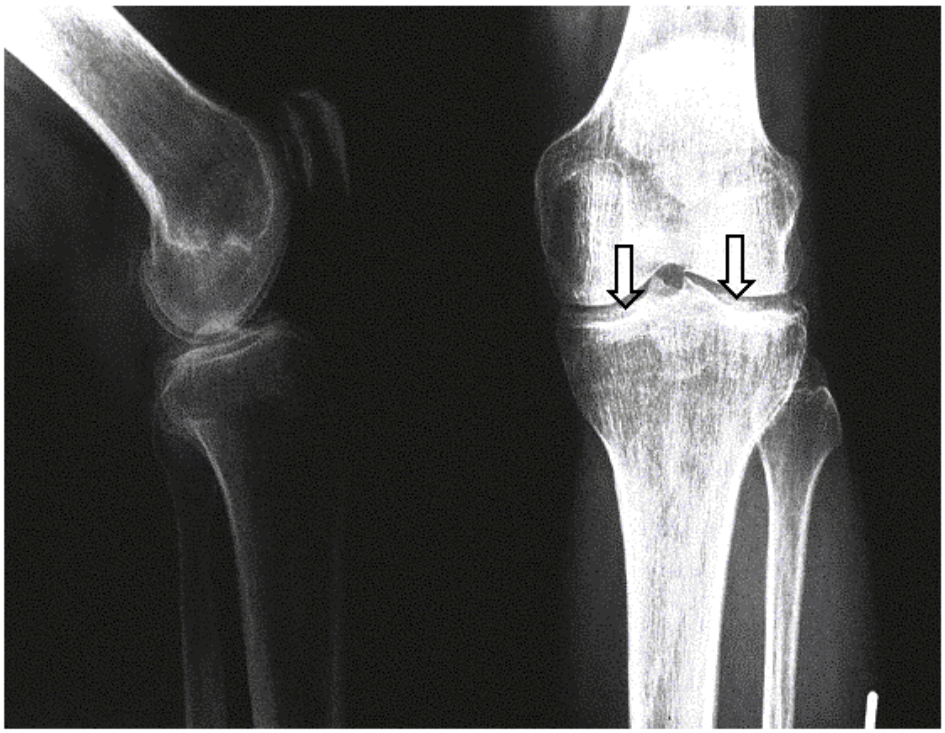

Figure 1. Radiography of the knee shows calcification of the menisci (arrows).

Taken together the electrolyte abnormalities suggested a renal tubular disorder. The arthralgias were interpreted in the context of calcium pyrophosphate crystal deposition.

Symptomatic treatment was begun with a non-steroidal anti-inflammatory drug (NSAID). The renal tubular disorder was treated with spironolactone in combination with a thiazide diuretic and supplementation of calcium and magnesium. Within several weeks the serum electrolytes returned to almost normal values (**Table 1**) and arthralgias and morning stiffness subsided.

Table 1. Composition of important laboratory findings. 1st values were obtained at admission, 2nd values 4 weeks after beginning of the treatment.

Marker	1st value	2nd value	Reference values
Arterial Blood Gas Analysis			
pH (37°C)	7.499	7.438	7.36-7.44
pCO_2 (37°C)	4.9 kPa	5.23 kPA	4.6-6.0 kPa
pO_2 (37°C)	16.59 kPa		12-13.3 kPa
HCO^-_3	28.4 mmol/l	25.9 mmol/l	22-26 mmol/l
BE	(+)5.4 mmol/l		(-)2.0-(+)2.0 mmol/l
Serum			
Potassium	2.8 mmol/l	3.4 mmol/l	3.5-4.5 mmol/l
Calcium (total)	2.06 mmol/l	2.3 mmol/l	2.1-2.6 mmol/l
Magnesium	0.37 mmol/l	0.42 mmol/l	0.65-1.00 mmol/l
Phosphate	0.86 mmol/l		0.6-1.3 mmol/l
Albumin	39.0 g/l	44.0 g/l	40-50 g/l
Creatinine	95 µmol/l	104 µmol/l	70-105 µmol/l
Alkaline Phosphatase	69 U/l		30-115 U/l
Trijodthyronine	4.9 pmol/l		2.8-7.1 pmol/l
Testosterone	15.5 nmol/l		8.2-35 nmol/l
Aldosterone	514 pmol/l		55-330 pmol/l
Parathyroid hormone	77.0 ng/l		12-72 ng/l
25-Hydroxy-Vit D	26.8 µg/l		10-42 µg/l
Telopeptide (ICTP)	5.9 µg/l		1.8-5.0 µg/l
Osteocalcin	4.19 µg/l		3.4-11.7 µg/l
Urine chemistry			
Potassium	55.6 mmol	87.8 mmol	35-90 mmol
Magnesium	6.06 mmol		3.0-5.0 mmol
Phosphate	18.88 mmol	24.55 mmol	12.9-42.0 mmol
Calcium	3.04 mmol	2.22 mmol	< 7.5 mmol
Aldosterone-Glucuronide	42 nmol/24h		6-36 nmol/24h
Ratio deoxypyridinoline /Creatinine	5.5 nmol/mmol		2.5-5.0 nmol/mmol

DISCUSSION

The described patient presents with an unusual combination of chondrocalcinosis and osteoporosis related to a renal tubular disorder, displaying features of both Bartter's and Gitelman's syndrome, as underlying disease. Bartter's syndrome is caused by impaired tubular reabsorption of sodium by the Na/K/2Cl cotransporter in the thick ascending limb of Henle. This results in increased distal delivery of sodium to the

collecting duct, favouring enhanced proton secretion, inducing metabolic alkalosis. In comparison, the molecular defect in Gitelman's syndrome is in the Na/Cl cotransporter residing in the distal tubule. Whereas in patients with Gitelman's syndrome hypocalciuria and hypermagnesiuria with hypomagnesemia is common, patients with Bartter's syndrome characteristically show hypercalciuria and usually normal serum magnesium (Gitelman et al., 1966; Kurtz, 1998), however, hypomagnesemia in patients with Bartter's disease has been previously reported (Bettinelli et al., 1992). Whereas in our patient the hypermagnesiuria and also the reported muscle cramps suggested Gitelman's syndrome, hypocalcemia and hypercalciuria rather indicated Bartter's disease. In conclusion, the exact molecular nature of the renal tubular transport defect in our patient remains elusive. However, the clinical findings suggest a link between the renal electrolyte disorder and the pathological skeletal findings. An association of hypomagnesemia with chondrocalcinosis has been suggested by several studies and case reports (Jones et al., 1992; Salvarani et al., 1989; Smilde et al., 1994). There has been some controversy over the association of Bartter's syndrome and chondrocalcinosis. Evidence has been presented indicating that previous reports of cases of Bartter's syndrome associated with chondrocalcinosis may actually rather be diagnosed as Gitelman's syndrome (Punzi et al., 1998).

Interestingly, bone densitometry in our patient revealed osteoporosis of the lumbar spine. Additionally, serum carboxy-terminal telopeptide of type I collagen (ICTP) and urine deoxypyridinoline were elevated, indicating bone resorption (Kushida et al., 1995; Seibel et al., 1993). Osteoporosis commonly progresses silently for long time periods until fractures occur, along with pain being frequently the only symptom of this disease. Conditions known to cause osteoporosis are of genetic, functional, environmental or endocrine origin (Sambrook et al., 1998). In our patient, genetic and functional disorders could be excluded on clinical grounds, and hyperthyroidism and hypogonadism by normal findings of the respective hormones. The patient history and biochemical markers did not reveal evidence of alcohol abuse, an important risk factor for osteoporosis. There were slightly increased levels for intact PTH, probably secondary to hypocalcaemia; however, levels of serum phosphate and alkaline phosphatase were normal. Hypercalciuria, as found in Bartter's syndrome, has been associated with osteoporosis (Laroche et al. 1994; Perry et al., 1982). Laroche et al. (1994) found hypercalciuria due to renal tubular disorders in a significant proportion of osteoporotic men. These tubular disorders were frequent among younger osteoporotic patients with a mean age of 45 +/- 8 years, warranting assessment of renal tubular function in these patients. On the other hand, because of the silent progression of osteoporosis for decades before the presentation of clinical features, individuals with hypocalcaemic renal tubular disorder should be screened by bone densitometry.

In summary, we reported on a patient with osteoporosis and chondrocalcinosis suffering from renal tubular dysfunction sharing clinical similarities with Bartter's and Gitelman's syndrome. Both osteoporosis, associated with hypercalciuria as occurring in Bartter's syndrome, and chondrocalcinosis, associated with Gitelman's syndrome, can be accounted for by the complex electrolyte changes due to the tubular disorder. Such association is supported by the rapid normalization of the electrolyte disturbances upon treatment with spironolactone and thiazide in combination with calcium and magnesium supplementation, accompanied by the disappearance of clinical symptoms.

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