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Hypocalciuric Hypercalcemia Due to Isolated Renal Granulomatous Disease

To the Editor:

Macrophages in granulomas produce 1-α hydroxylase, which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (1,25OH-D).[1] Hence, in granulomatous diseases, hypercalcemia is a common complication and is generally hypercalciuric.[2,3] Here, we present a case of isolated renal granulomatous disease with hypocalciuric hypercalcemia.

A 79-year-old male with chronic kidney disease developed hypercalcemia with an albumin-corrected serum calcium concentration (c[Ca]) of 11.1 mg/dL (normal range: 8.8-10.1 mg/dL) and was referred to our hospital. Because his serum creatinine concentration (s[Cr]) increased from 1.7 to 3.8 mg/dL within a month and urinalysis revealed high levels of β_2-microglobulin (7688 μg/L; normal range: <289 μg/L) and N-acetyl-β-D-glucosaminidase (47.5 U/L; normal range: <11.5 U/L), a renal needle biopsy was performed.

Light microscopy examination of the biopsy samples revealed interstitial non-necrotizing granulomatous lesions containing multinucleated giant cells (Figure). Although sarcoidosis was suspected, computed tomography did not detect lymph node enlargement in the chest and abdomen, and serum levels of angiotensin-converting enzyme (18.4 U/L; normal range: 7.0-25.0 U/L) and 1,25OH-D (58 pg/mL; normal range: 20-60 pg/mL) were not elevated. Furthermore, urine calcium excretion was only 84 mg per gram of creatinine (mg/gCr), and plasma levels of intact parathormone (8 pg/mL; normal range: 10-65 pg/mL) and parathormone-related peptide (<1.1 pmol/L; normal range: <1.1 pmol/L) were not elevated.

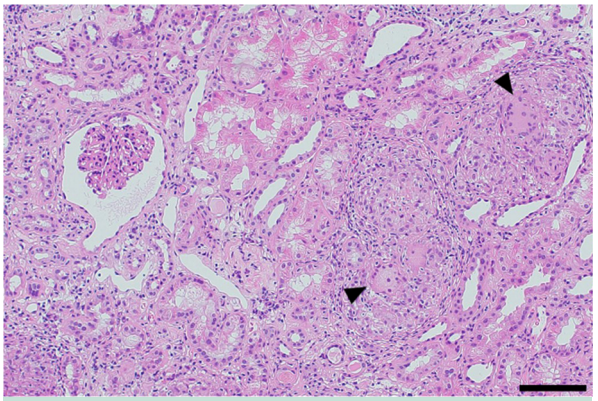

Figure Histological findings of renal biopsy. Hematoxylin and eosin staining showing non-necrotizing granulomatous lesions with multinucleated giant cells (arrowheads). Scale bar: 100 μm.

Based on the histological findings, oral prednisolone therapy was initiated at a dose of 40 mg/d. One week later, urine calcium excretion increased to 271 mg/gCr and c[Ca] decreased to 10.5 mg/dL. Another week later, c[Ca] further decreased to 9.4 mg/dL and s[Cr] decreased to 1.7 mg/dL.

With no sign of extrarenal granulomatous disease, the patient was diagnosed with isolated renal granulomatous disease. As noted in our patient, hypercalcemia is frequently observed with normal serum 1,25OH-D levels in granulomatous diseases, including sarcoidosis, a systemic granulomatous disease.[2–4] However, because the 1,25OH-D levels would decrease in the presence of hypercalcemia, they are considered to be inadequately high,[4] and hypercalcemia in granulomatous diseases would be attributed to increased gastrointestinal calcium absorption by 1,25OH-D.[5,6] Therefore, it is generally accompanied by hypercalciuria.[2,3]

In contrast to most granulomatous diseases, which have hypercalciuric hypercalcemia, this case had hypocalciuric hypercalcemia. This could be attributed to increased renal tubular calcium absorption. In this case, the 1,25OH-D converted by renal granulomas may have stayed intrarenally and increased renal tubular, but not gastrointestinal, calcium absorption.[6] A decrease in c[Ca] accompanied by an increase in urine calcium excretion through prednisolone therapy supported this presumption, even without confirmation of 1,25OH-D synthesis in the renal granulomas, which could not be confirmed due to a lack of molecular measures of local

Abbreviations: 1,25OH-D, 1,25-dihydroxyvitamin D; c[Ca], albumin-corrected serum calcium concentration; s[Cr], serum creatinine concentration

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Requests for reprints should be addressed to Masayuki Tanemoto, MD, PhD, Division of Nephrology, Department of Internal Medicine, International University of Health and Welfare School of Medicine, 13-1 Higashi-Kaigan-Cho, Atami, Shizuoka 413-0012, Japan.

E-mail address: mtanemoto-tky@umin.ac.jp

tissue vitamin D levels. While the glucocorticoid action of prednisolone may have increased urine calcium excretion and decreased c[Ca],[7] these findings suggest that renal granulomatous disease should be suspected in cases of hypocalciuric hypercalcemia wherein heredity is an unlikely cause.

Masayuki Tanemoto, MD, PhD[a,b]
Takahide Kimura, MD[a,b]
[a]*Division of Nephrology, Department of Internal Medicine, International University of Health and Welfare School of Medicine, Atami, Shizuoka, Japan*
[b]*Dialysis Unit, Shin-Kuki General Hospital, Kuki, Saitama, Japan*

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