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CASE REPORT

# Tumoral calcinosis in a patient with hypoparathyroidism, sensorineural deafness, and renal dysplasia syndrome undergoing hemodialysis

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### Key Clinical Message

We describe a hemodialysis patient with hypoparathyroidism due to HDR (hypoparathyroidism, sensorineural deafness, and renal dysplasia) syndrome caused by GATA3 mutation. She presents tumoral calcinosis which is a rare complication of end-stage renal failure. A novel mutation of GATA3 is identified in this patient.

### Keywords

*GATA3* mutation, HDR syndrome, hemodialysis, hypoparathyroidism, tumoral calcinosis.

## Case Report

Hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome (MIM 146255) is a rare autosomal dominant disease characterized by hypoparathyroidism, sensorineural deafness, and renal dysplasia due to a heterozygous germline mutation of the *GATA3* gene located on chromosome 10p15 [1]. The hypoparathyroidism is characterized by symptomatic or asymptomatic hypocalcemia with low or undetectable serum levels of parathyroid hormone (PTH). The renal phenotype of HDR syndrome has a variable expression, which includes presence or absence of symmetry, renal agenesis, and renal dysplasia; patients with HDR syndrome often develop end-stage renal failure requiring dialysis due to renal abnormalities [2]. We present a case of tumoral calcinosis in a patient with HDR syndrome undergoing hemodialysis. Furthermore, a novel G289R mutation in *GATA 3* is identified in this report.

A 58-year-old Japanese woman with a 4-year history of hemodialysis therapy for renal dysplasia was admitted to our hospital for evaluation of hard masses on the fingers. She had right renal hypoplasia and bilateral sensorineural deafness, identified when she was aged 36 years. Before starting hemodialysis, asymptomatic hypocalcemia and hyperphosphatemia were found upon analysis of her laboratory data, but no further examinations were performed; no treatment for hypocalcemia, including calcium carbonate or active vitamin D sterols, were prescribed. After starting hemodialysis, serum phosphate levels were consistently elevated to 9.0–12.0 mg/mL because of poor dietary phosphorus restriction. Calcium-containing phosphate binders (calcium carbonate) were used to reduce phosphate levels, and serum calcium levels were elevated to 7.5–9.3 mg/dL. The mean serum calcium × phosphate product was markedly increased to 88 $mg^2/dL^2$. Reduction in dialysate calcium concentration to 1.25 mmol/L was not effective. Serum intact PTH (iPTH) levels were consistently extremely low, not more than 5 pg/mL, from the beginning of hemodialysis. Three months after initiation of hemodialysis, she noted a painless mass palpable around her finger joints on both hands, without antecedent trauma. Radiography revealed multilobulated calcified

masses, leading to a diagnosis of tumoral calcinosis (Fig. 1A). Laboratory data on admission were as follows: albumin, 29 g/L; total alkaline phosphatase (ALP), 135 IU/L; calcium, 9.4 mg/dL; albumin-adjusted calcium using serum albumin (calcium [mg/dL] − albumin [g/dL] ± 4.0), 10.5 mg/dL; phosphate 9.3 mg/dL; calcium × phosphate product, 98 $mg^2/dL^2$; iPTH < 1.4 pg/mL; serum level of 1,25-dihydroxycholecalciferol, 7 ng/L (reference range, 20–60 ng/L); 25-hydroxycholecalciferol, 16.9 μg/L: magnesium, 2.3 mg/dL (reference range 1.7–2.3 mg/dL); and bone-specific ALP, 11.5 U/mL (reference range, 9.6–35.4 U/mL). She has never used aluminum-containing phosphate binders, though the serum aluminum level was not available. The clinical features of sensorineural deafness and right renal hypoplasia suggested HDR syndrome. A study of the patient's family members was not possible, except for her mother, who exhibited no specific features of HDR syndrome. After obtaining the patient's written informed consent, we performed genetic analysis of *GATA3* using peripheral blood leukocytes, as described previously [3]. This study was approved by the institutional review board of Toranomon Hospital. A heterozygous mutation (G289R) (Fig. 1C, arrow) in exon 4 located within the zinc finger 1 domain of *GATA3* was detected. As this mutation has not previously been reported in HDR syndrome patients, we investigated the functional changes resulting from this mutation using a luciferase reporter gene assay system, as described previously [3]. Transfection of wild-type (WT)-GATA3 cDNA along with the reporter vector containing GATA response elements induced luciferase activity (Fig. 1D). In contrast, the mutant (MT)-GATA3 vector containing the G289R mutation was less potent in activating transcription, similar to C1063del, a previously reported inactivating mutation of *GATA3* found in patients with HDR syndrome [3]. Thus, G289R in *GATA3* represents a loss-of-function mutation. With strict restriction of dietary phosphorus and replacement of calcium carbonate with a noncalcium-containing binder (sevel-

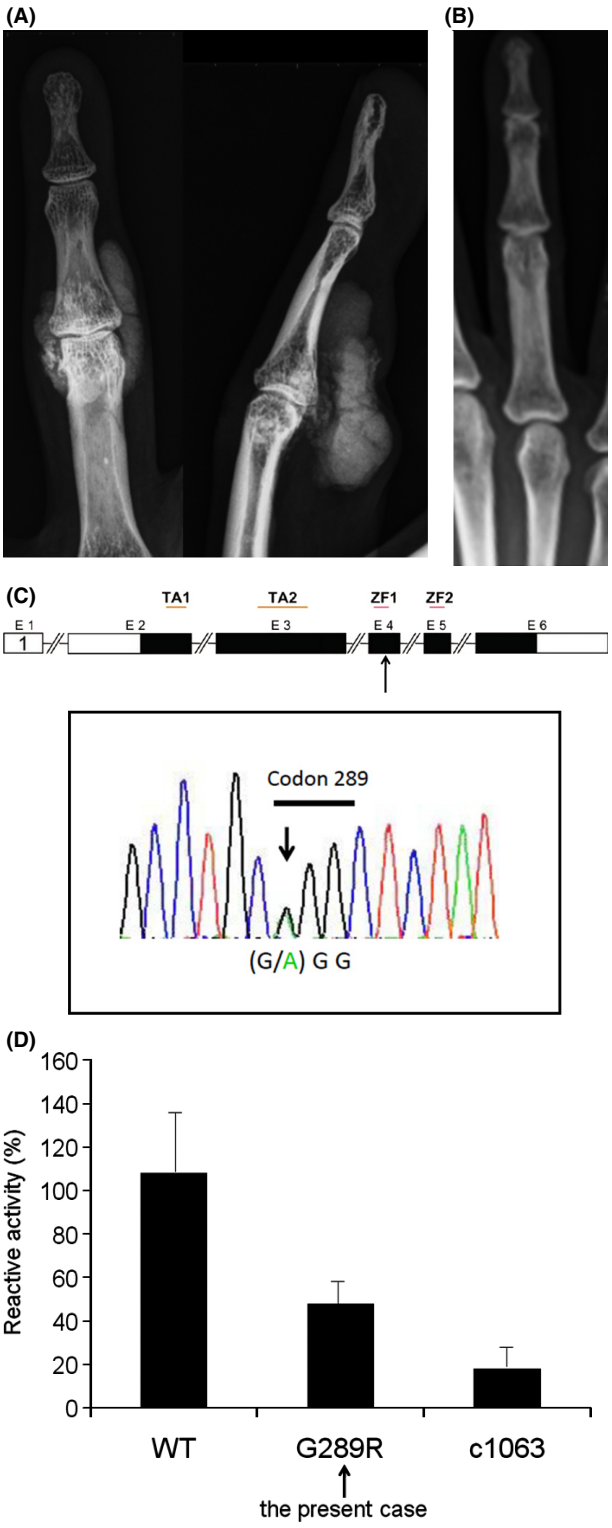


**Figure 1.** (A) Radiographs of the tumor-like calcified masses around the right and left proximal interphalangeal (PIP) joints. (B) With strict serum calcium and phosphorus control, tumoral calcinosis disappeared over a period of 3 years. (C) The *GATA3* gene consists of exons 1–6 (E1–E6) and encodes two transactivating domains (TA1 and TA2) and two zinc finger domains (ZF1 and ZF2). The black and white boxes denote the coding regions and the untranslated regions, respectively. The chromatograms in this patient show the presence of a heterozygous R289G (GGG to AGG) mutation in exon 4. (D) Transactivating activity of the G289R mutant *GATA3* gene product was examined compared with a positive control of wild-type *GATA3* (WT-GATA3). Transient expression in COS7 cells of WT-GATA3 cDNA stimulated transcriptional activity of the GATA-response element-containing reporter gene estimated using luciferase activity. In contrast, the mutants *GATA3* and G289R showed significantly less potential to activate transcription of the reporter gene.

amer), combined with prolongation of dialysis time from 4 to 5 h, the patient's serum calcium and phosphate levels were gradually reduced to 7.0–8.0 and 4.0–5.0 mg/dL, respectively. To prevent hypocalcemia, we prescribed low-dose calcium citrate malate to maintain serum calcium levels at 8.0–9.0 mg/dL. The calcium × phosphate product level was well controlled at $<50$ $mg^2/dL^2$, although serum iPTH remained at a consistently low level (<20 pg/mL). Over a period of 3 years, tumoral calcinosis on her fingers disappeared completely (Fig. 1B).

The clinical characteristics of HDR syndrome are heterogeneous among individuals. Ali et al. reported a series of clinical findings in 29 HDR patients in 21 families [2]. In their study, 2 HDR patients developed end-stage renal failure. The prevalence of HDR patients who develop renal dysfunction resulting in hemodialysis and their clinical descriptions has not been reported.

Tumoral calcinosis was originally described as a familial condition characterized by solitary or multiple painless, periarticular soft-tissue calcium masses [4]. The generally accepted mode of transmission is autosomal dominant with variable expressivity and has been shown to result from mutations in three genes: fibroblast growth factor-23 (*FGF23*), coding for a potent phosphauretic protein; *KL* coding Klotho, a coreceptor for FGF23; and *GALNT3*, encoding a glycosyltransferase responsible for FGF23 O-glycosylation [4]. Calcified masses, which are similar to familial tumoral calcinosis, are also observed in acquired conditions such as chronic kidney disease. Tumoral calcinosis in dialysis patients is rare, and its frequency ranges from 0.5% to 3% [5]. The most important pathogenic factors in tumoral calcinosis in dialysis patients are an increased calcium × phosphate product ($>70$ $mg^2/dL^2$) mainly related to secondary hyperparathyroidism [5]. In contrast, low bone turnover is also involved in its pathogenesis. In this condition, the buffering capacity of calcium and phosphate in bone is diminished, producing conditions that favor extraosseous calcification. The use of calcium carbonate or vitamin D sterols may easily produce hypercalcemia, further PTH suppression, and an increased risk of extraosseous calcium deposits.

Tumoral calcinosis in our patient developed after initiation of hemodialysis therapy. She did not show hyperparathyroidism nor Vitamin D depletion. We believe that high calcium × phosphate product induced by poor dietary control of phosphorus and administration of calcium carbonate for control of serum phosphate levels is the main pathogenesis. Furthermore, a total lack of PTH activity caused by HDR syndrome facilitates the diminishment of calcium–phosphate influx and efflux from bone, resulting in the development of tumoral calcinosis. Effective control of calcium and phosphate levels by careful dietary phosphorus control, prolongation of dialysis time, and use of noncalcemic phosphate binders enabled mobilization of calcium and phosphate and led to the disappearance of tumoral calcinosis.

## Conflict of Interest

None declared.

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