RESEARCH

The first case of primary hypertrophic osteoarthropathy with soft tissue giant tumors caused by HPGD loss-of-function mutation

Qianqian Pang¹,², Yuping Xu¹,³, Xuan Qi¹, Yan Jiang¹, Ou Wang¹, Mei Li¹, Xiaoping Xing¹, Ling Qin² and Weibo Xia¹

¹Department of Endocrinology, Key Laboratory of Endocrinology, Ministry of Health, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China
²Musculoskeletal Research Laboratory and Bone Quality and Health Assessment Centre, Department of Orthopedics & Traumatology, The Chinese University of Hong Kong, Hong Kong SAR, Hong Kong
³Department of Endocrinology, The First Affiliated Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

Correspondence should be addressed to L Qin or W Xia: lingqin@cuhk.edu.hk or xiaweibo8301@163.com

Abstract

Background: Primary hypertrophic osteoarthropathy (PHO) is a rare genetic multi-organic disease characterized by digital clubbing, periostosis and pachydermia. Two genes, HPGD and SLCO2A1, which encode 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and prostaglandin transporter (PGT), respectively, have been reported to be related to PHO. Deficiency of aforementioned two genes leads to failure of prostaglandin E2 (PGE2) degradation and thereby elevated levels of PGE2. PGE2 plays an important role in tumorigenesis. Studies revealed a tumor suppressor activity of 15-PGDH in tumors, such as lung, bladder and breast cancers. However, to date, no HPGD-mutated PHO patients presenting concomitant tumor has been documented. In the present study, we reported the first case of HPGD-mutated PHO patient with soft tissue giant tumors at lower legs and evaluated the efficacy of selective COX-2 inhibitor (etoricoxib) treatment in the patient.

Methods: In this study, we summarized the clinical data, collected the serum and urine samples for biochemical test and analyzed the HPGD gene in our patient.

Results: A common HPGD mutation c.310_311delCT was identified in the patient. In addition to typical clinical features (digital clubbing, periostosis and pachydermia), the patient demonstrated a new clinical manifestation, a giant soft tissue tumor on the left lower leg which has not been reported in HPGD-mutated PHO patient before. After 6-month treatment with etoricoxib, the patient showed decreased PGE2 levels and improved PHO-related symptoms. Though the soft tissue tumor persisted, it seemed to be controlled under the etoricoxib treatment.

Conclusion: This finding expanded the clinical spectrum of PHO and provided unique insights into the HPGD-mutated PHO.

Key Words
- primary hypertrophic osteoarthropathy
- PHO
- HPGD mutation
- soft tumor
- COX2 selective inhibitor treatment

Introduction

Primary hypertrophic osteoarthropathy (PHO; MIM 167100), also known as pachydermoperiostosis or idiopathic hypertrophic osteoarthropathy, is a rare genetic multi-organic disease characterized by digital clubbing, periostosis and pachydermia. Accompanying abnormalities include sebaceous hyperplasia, hyperhidrosis, acro-osteolysis, and effusions and pain of large joints (1, 2). Additional developmental anomalies,
seen in a proportion of PHO patients, include patent ductus arteriosus and myelofibrosis (3, 4).

To date, two genes have been reported to be associated with PHO: hydroxyprostaglandin dehydrogenase (HPGD; MIM 601688), which encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), and solute carrier organic anion transporter family, member 2A1 (SLCO2A1; MIM 601460), which encodes a prostaglandin transporter (1, 5). The pathogenesis and inherited pattern were controversial for a long time until the year 2008, and Uppal et al. identified the mutation of HPGD as the primary causative factor of PHO (1). Subsequently, Zhang et al. (5) confirmed the second gene SLCO2A1 to be responsible for PHO. According to the molecular findings, PHO has been categorized into two subtypes: (1) hypertrophic osteoarthropathy, primary, autosomal recessive, type 1 (PHOAR1; MIM 259100), caused by HPGD deficiency and (2) hypertrophic osteoarthropathy, primary, autosomal recessive, type 2 (PHOAR2; MIM 614441), caused by SLCO2A1 deficiency. Both HPGD and SLCO2A1 deficiency can independently lead to failure of PGE₂ degradation, resulting in elevated levels of prostaglandin E2 (PGE₂) in the circulation, which is thought to contribute to the pathogenesis for PHO (1, 6).

PHO is a clinically heterogeneous disease. The onset age of PHO is bimodal distribution. Peaking onset age of clinical manifestations is usually the first year of life in PHOAR1 with HPGD mutations, and at puberty in PHOAR2 with SLCO2A1 mutations (6). Sefert et al. (7) revealed that manifestations of bones and joints found in patients with homozygous mutations in the HPGD, usually appear earlier than those in the SLCO2A1, suggesting the clinical heterogeneity between the two subtypes of PHO.

It is widely acknowledged that PGE₂ plays an important role in the development of tumors. PGE₂ can stimulate cell proliferation, angiogenesis and motility while inhibiting apoptosis and immune surveillance (8, 9, 10). Reduced 15-PGDH and SLCO2A1 are believed to contribute to elevated levels of PGE₂ in the circulation thereby leading to the pathogenesis of these tumors (11, 12, 13, 14). However, in humans, reports of HPGD and SLCO2A1 mutation cases have only been focused on the typical features such as digital clubbing, periostosis and pachydermia. Till 2014, Guda et al. (15) reported a French-Canadian family with SLCO2A1 mutation presenting digital clubbing and early-onset colon neoplasm, suggesting a link between PHO and tumors. 15-PGDH is the major enzyme responsible for prostaglandin degradation. Numerous studies have demonstrated a tumor suppressor activity of 15-PGDH in a number of different tumors, such as lung, bladder and breast cancer (16, 17, 18). Whereas, to date, no HPGD-mutated PHO patients presenting concomitant tumor have been documented.

Up to now, no standard treatment has been approved for PHO due to the small number of patients with PHO at most clinical centers. There are some case reports with varying therapeutic option and response, and the treatments are mostly focused on alleviation of symptoms, including nonsteroidal anti-inflammatory drugs (NSAIDS), pamidronate and tamoxifen citrate to relieve painful osteoarthropathy (19, 20). Given that the increased circulating PGE₂ levels is responsible for pathogenic mechanism of PHO, cyclo-oxygenase (COX) inhibition may represent a targeted therapeutic option. Recently, COX-2 selective inhibitors, which inhibit the COX-2 enzyme and thereby suppress PGE₂ biosynthesis, represent promising treatment options for PHO. A few studies have shown that etoricoxib, a novel COX-2 selective inhibitor, has a positive therapeutic effect on PHO patients in terms of decreased urinary PGE₂ levels and improvement of clinical phenotypes including pachydermia, clubbing finger and joint swelling (21, 22, 23).

Here we reported the first case of a Chinese HPGD-mutated PHO patient with soft tissue giant tumors at bilateral lower legs, as well as evaluated the efficacy of selective COX-2 inhibition (etoricoxib) treatment in this patient.

Methods and materials

Human subjects

This study was approved by the Local Ethics Committee of the Department of Scientific Research at Peking Union Medical College Hospital (PUMCH). The Chinese PHO patient signed informed consent documents before entering the study.

Biochemical parameters

The patient was admitted into our hospital and went through detailed clinical, biochemical and radiographic investigation. For biochemical analysis, fasting blood samples and 24-h urine were collected. Serum calcium (Ca), serum phosphate (Pi), serum alkaline phosphatase (ALP), serum creatinine (SCR), erythrocyte sedimentation rate (ESR), hypersensitive C reactive protein (hsCRP), interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured spectrophotometrically using routine
assays available at the central laboratory of PUMCH. Serum intact parathyroid hormone (iPTH) and beta- C-terminal telopeptide of type I collagen (β-CTX) were measured by an automated Roche electrochemiluminescence system (Roche Diagnostics). Serum and urinary PGE₂ and PGEM (a metabolite of PGE₃) levels were measured by competitive enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Cayman Chemicals). The measuring ranges of ESR, hsCRP, IL-6, TNF-α, PTH, β-CTX, PGE₂ and PGEM were 1–140 mm/h, 0.15–20 mg/L, 2–1000 pg/mL, 1.7–1000 pg/mL, 1.2–5000 pg/mL, 0.01–6.00 ng/mL, 7.8–1000 pg/mL and 0.39–50 pg/mL, respectively. The intra-assay coefficients of variation were <5% for ESR, 0.7% for hsCRP, 3.5–6.2% for IL-6, 2.6–3.6% for TNF-α, 1.2% for iPTH, 2.0% for β-CTX, 3.7% for PGE₂ and 5.5% for PGEM.

**Imaging techniques**

X-ray radiography of both hands and legs were performed to assess bony deformities. Magnetic resonance imaging (MRI) of the bilateral legs was performed to confirm the X-ray findings and evaluate the giant tumors at patient’s lower legs. Computed tomographic angiography (CTA, SOMATON Force, Siemens Healthineers) was conducted at the tumor sites to clarify the tumor source and vascular perfusion.

**Area bone mineral densities (BMD)**

Area bone mineral densities of lumbar spine and proximal femur were measured with a dual energy X-ray absorptiometry (Prodigy Advance, GE Lunar Corporation).

**Mutational analysis**

Whole blood was obtained from the patient. Genomic DNA was extracted from peripheral white blood cells using the DNA Extraction Kit (QIAamp DNA, Qiagen) according to the manufacturer’s instructions. The seven exons of HP GD were amplified through PCR with a set of primers designed by Gene Runner Primer Analysis Software. The amplified products were sequenced by an automated sequencer (ABI 373XL sequencer, Applied Biosystems) according to the manufacturer’s recommendation. Putative mutations were analyzed and compared using the Basic Local Alignment Search Tool (Blast).

**Bioinformatics analysis**

The identified mutation in HP GD gene was analyzed at the protein level. Protein modeling was conducted based on the data of 15-PGDH structure in Protein Date Bank (PDB ID: 2GDZ, http://www.rcsb.org), and the mutational-related residues were positioned in the constructed 3D structural model (24) using the PyMOL Viewer 1.8.6 (free download from https://pymolwiki.org).

**Results**

**Clinical findings**

The 41-year-old patient was born to healthy consanguineous parents. Widening of distal phalanges of fingers, hyperhidrosis of hands and facial furrowing were noted during infancy. He complained of frequent pain in bilateral knees after having a cold. From the age of 35 years, he had swelling in knees and ankles but denied any bone pain. One year later, he noticed a soft tumor at his left leg, and the size of the tumor increased rapidly in the following years. At the age of 41 years, he was admitted to our clinic with complains of a giant tumor at left leg. Physical examination showed digital clubbing (Fig. 1A), oily, thickened and furrowed face (Fig. 1B), palmar plantar hyperhidrosis and palmar plantar hyperkeratosis. Swelling was found in bilateral wrists and knees (circumference of left and right knee was 37.0 cm and 38.0 cm, respectively). He suffered from a total of three soft tumors at bilateral legs, and the most giant one located at left lower leg (10 × 12 cm, circumference 44.5 cm), and the other two smaller tumors located at right lower leg (Fig. 1C). He had no cardiac, pulmonary, hepatic disease, as well as delayed closure of cranial suture, anemia or hypoalbuminemia. He denied any gastrointestinal discomfort. The laboratory findings were shown in Table 1. Area bone density of lumbar spine and proximal femur were in normal range. Radiological examination of both hands and legs showed acro-osteolysis on distal phalanges of fingers (Fig. 2A) and periostosis along long bones (Fig. 2B and C). Besides, X-ray of bilateral legs revealed massive soft tissue swelling of calf (Fig. 2B and C). MRI of legs confirmed the plain radiographic findings and also showed subchondral cysts, diffuse synovial hypertrophy and effusion in bilateral knees (Fig. 2D and E). Additionally, MRI imaging showed round hyperdense foci around medial of the midshaft of the left tibia (6.2 × 11.2 × 10.6 cm), as well as round hyperdense foci at the right upper fibular
Q Pang et al. PHO patients with soft tissue giant tumor caused by HPGD mutation

739

8:6

Histological evaluation of the tumor tissue revealed a benign tumor with irregularly curved immature woven bone trabeculae and proliferative fibrous granulation tissues invading among the trabecular bones (Fig. 3). PHO diagnosis was made by typical features including digital clubbing, hyperhidrosis, periostosis and acro-osteolysis, as well as the increased levels of serum PGE$_2$. The patient has two siblings, and all of his relatives were healthy without any typical PHO symptoms.

**The treatment of patient**

The patient was treated with selective COX-2 inhibitor (etoricoxib, 60mg once daily, Merk Sharp & Dohme Corp USA) and re-evaluated at the time point of 6 months. After re-evaluation, we found etoricoxib treatment led to the reduction of swelling in knees (circumference decreased from 38 to 37.1 cm) and ankles than it was before etoricoxib treatment, though facial furrowing appearance persisted. The soft tissue mass in bilateral legs persisted but did not evolve since etoricoxib treatment. Serum and urinary PGE$_2$ levels, inflammatory cytokines and bone turnover markers all decreased after treatment. The levels of the biochemical markers before and after treatment were shown in Table 1. MRI of the bilateral knees showed remission of synovitis.

**Mutational analysis of HPGD**

Direct sequencing of genomic DNA indicated that the patient carried a homozygous mutation c.310_311delCT. This mutation caused frameshift after 103T and created a premature TAA stop signal at codon 106 which resulted in a truncated protein. The mutation-related residues (103T)

---

**Figure 1**

The clinical features of the HPGD-mutated PHO patient. (A) Digital clubbing. (B) Oily, thickened and furrowed face. (C) A soft tissue giant tumor on the left lower leg (white arrow), two smaller tumors on the right leg (red arrow).

**Table 1** Laboratory findings of the PHO patient before and after etoricoxib treatment.

|                  | Before treatment | After treatment | Reference range |
|------------------|------------------|----------------|-----------------|
| Routine biochemical markers |                  |                |                 |
| ALT (U/L)        | 44               | 16             | 9–50            |
| SCR (µmol/L)     | 68               | 62             | 59–104          |
| Ca (mmol/L)      | 2.22             | 2.17           | 2.13–2.70       |
| Pi (mmol/L)      | 1.16             | 1.02           | 0.81–1.45       |
| ALP (U/L)        | 130              | 102            | 45–125          |
| iPTH (pg/mL)     | 56.3             | 47.9           | 12–65           |
| β-CTX (ng/mL)    | 0.827            | 0.654          | 0.26–0.512      |
| Inflammatory cytokines |                |                |                 |
| ESR (mm/h)       | 6                | NA             | 0–15            |
| hsCRP (mg/L)     | 33.4             | 0.78           | 0–3             |
| IL-6 (pg/mL)     | 9.0              | 2.0            | <5.9            |
| TNF-α (pg/mL)    | 4.7              | 4.8            | <8.1            |
| Specific biochemical markers |            |                |                 |
| Serum PGE2 (pg/mL) | 316             | 231            | 28.7–308.2 (26) |
| Serum PGEM (pg/mL) | 13.3            | 24.1           | 0.5–17.2 (26)   |
| Urinary PGE2 (ng/mmol cr) | 618             | 215            | 36.4–85.5 (25)  |
| Urinary PGEM (ng/mmol cr) | 4.27            | 3.27           | 23–52.8 (25)    |

Abnormal findings were indicated in bold.

ALP, serum alkaline phosphatase; ALT, alanine aminotransferase; β-CTX, beta-C-terminal telopeptide of type I collagen; Ca, calcium; ESR, erythrocyte sedimentation rate; hsCRP, hypersensitive C reactive protein; IL-6, interleukin 6; NA, not available; Pi, phosphate; PTH, parathyroid hormone; Scr, serum creatinine; TNF-α, tumor necrosis factor-α.

This work is licensed under a Creative Commons Attribution 4.0 International License.

https://doi.org/10.1530/EC-19-0149

© 2019 The authors Published by Bioscientifica Ltd

https://ec.bioscientifica.com
and predicted truncated protein of HPGD gene were shown in Fig. 4. The deletion c.310_311delCT has been reported in some Asian PHO families (19, 22, 25), which seems to be a hotspot mutation in Asian PHO patients.

**Discussion**

PHO is a rare genetic disease featured by digital clubbing, periostosis, pachydermia and acro-osteolysis, which has been linked to the failure of prostaglandin metabolism. Defects of two genes have been confirmed to be responsible for this disease: HPGD and SLCO2A1, which encodes 15-PGDH and prostaglandin transporter (PGT), respectively (1, 5). Under normal conditions, PGE₂ is metabolized and cleared through two main steps: (1) selective uptake of PGE₂ across the plasma membrane by PGTs, including SLCO2A1, SLCO3A1, SLCO4A1. (2) degradation of PGE₂ inside the cell by 15-PGDH into PGEM (26). 15-PGDH is the main enzyme in prostaglandin metabolism. Patients with HPGD loss-of-function mutations present elevated PGE₂ levels (1, 27). Consistently, in the current study, our patient showed an increased level of serum and urinary PGE₂ (Table 1).

To date, HPGD mutations have been reported in 47 families, of which 20 were from Southern or Western Asia (1, 3, 19, 27, 28, 29, 30). In the present study,
a previously known HPGD mutation (c.310_311delCT) was identified in our patient. The mutation c.310_311delCT, which contributed to a frameshift after codon 104 and resulted in the loss of protein acceptor site as well as the putative substrate-binding site, is currently considered to be the most common mutation in Asian familial cases (19). In Yuan’s study, this common mutation was found in all the nine reported Chinese patients, indicating the high frequency of c.310_311delCT mutation in Chinese PHO patients (25).

The HPGD gene encodes a helical protein, consists of 266 amino acids, which belongs to the member of the short-chain dehydrogenase family (SDR) family (31). Generally, SDRs are divided into two larger families, ‘classical’ with 250-odd residues and ‘extended’ with 350-odd residues. 15-PGDH belongs to the ‘classical’ SDR family. Specifically, the structure of 15-PGDH (the ‘classical’ SDR enzyme) includes N-terminal transmembrane domains, C-terminal transmembrane domains, nucleotide-binding region, active site, central β-sheet and the helix. Previous studies have revealed that the active sites Ser138, Tyr151 and Lys155 are the most conserved residues essential for catalytic activity of 15-PGDH. Tyr151 functions as the catalytic base, whereas Ser138 stabilizes the substrates, and Lys155 forms hydrogen bonds with the nicotinamide ribose moiety to promote proton transfer (32, 33). Niesen et al. (24) have constructed a 3D structure of human 15-PGDH by homology modeling technique. The deletion mutation c.310_311delCT encodes a truncated protein lacking 160 amino acids of the C-terminal domain, which might interfere the stability and function of 15-PGDH structure. Ultimately, this mutation would result in loss of function of the enzyme since the most important residues (Ser138, Tyr151 and Lys155) were all absent from the protein (Fig. 4). In view of the fact that 15-PGDH is the main enzyme in prostaglandin metabolism, the alteration of the 15-PGDH structure may be the cause of the variations in clinical phenotypes in PHO patients.

We reviewed all 51 HPGD mutant patients (PHOAR1) reported before and found almost all of these PHOAR1 patients have digital clubbing (50/51, 98%) and periostosis (51/51, 100%). Besides, accompanying abnormalities such as hyperhidrosis (41/51, 80.4%), joint swelling (30/51, 58.8%), various forms of pachydermia (28/51, 54.9%) and arthralgia (22/51, 43.1%) have also been seen in a proportion of the PHOAR1 patients (1, 21, 22, 23, 25, 29, 34, 35, 36). Consistent with Hou’s study (27), gastrointestinal complications, peptic ulcer, chronic gastritis, anemia and myelofibrosis which were only presented in PHOAR2 patients, were absent in these PHOAR1 patients. In keeping with previous findings of the reported HPGD-mutated patients, the dermatoskeletal features of the patient in this study were typical for PHOAR1. The patient presented an early-onset age in infancy, which was similar to those extensively reported in previous HPGD-mutated PHO patients (6). Additionally, the patient had typical phenotypes of digital clubbing, periostosis, pachydermia, hyperhidrosis and arthropathy but denied any gastrointestinal complications, peptic ulcer, chronic gastritis, anemias and myelofibrosis syndromes.

It was well known that PGE₂ could stimulate the activity of both osteoclasts and osteoblasts, causing the enhancement of bone resorption and new bone formation, which might be related to PHO skeletal manifestations such as acro-osteolysis and periostosis (1). Jajic et al. (37) reviewed all of the reported 76 PHO patients and found all of these patients had periosteal reaction along the long bones and 23.7% of these patients had acro-osteolysis. Because the levels of bone turnover markers were not investigated in these patients, the association between PGE₂ and bone homeostasis were still unknown in PHO patients. In our study, the patient showed acro-osteolysis at distal phalanges of the fingers (Fig. 2A) and periostosis.
at the shafts of tubular bones (Fig. 2B and C). Biochemical test of the patient showed elevated levels of β-CTX and ALT. Skeletal X-ray findings in combination with the increased levels of bone turnover markers, suggested that though area bone mineral densities (aBMD) were within the normal range, there might be still some skeletal changes independent of aBMD measured by DXA in PHO patients.

As discussed earlier, nearly half of PHOAR1 patients presented osteoarticular manifestations, including joint swelling (30/51, 58.8%) and arthralgia (22/51, 43.1%), but joint impairment assessment through radiographic imaging of these patients was lacking. Literature review provides MRI examination results in six PHO patients, but the regions of interest (ROI) of MRI were focused on the bones rather than the joints. Pineda et al. (38) demonstrated remodeling and thickening of cortical bone and tortuous intraosseous vascular channels. Adams et al. (34) found transverse long bone expansion with periosteal thickening using gadolinium-enhanced MR images. In the present study, MRI of bilateral legs was performed in the PHO patient. Both bones and joints were scanned and evaluated in the MRI examination and the results showed thickening of cortical bones and bone marrow edema in femurs and tibias (Fig. 2D). Moreover, joint swelling, subchondral cysts, diffuse synovial hypertrophy and effusion were also seen in knee joint (Fig. 2E), suggesting joint impairment of the patient.

It is worth mentioning that the patient had soft tissue tumors at bilateral lower legs, which has not been reported in PHOAR1 patients before. Studies have revealed that 15-PGDH expression was reduced in colon, breast, gastric and lung cancers and restoration of 15-PGDH could inhibit tumorigenesis in xenografts, indicating that 15-PGDH was a tumor suppressor in these tumors as well as played an essential role in regulating tumor development and progression (16, 17, 18). A work from Rogenski’s laboratory (17) showed that 15-PGDH knockdown in 9027 shRNA lentivirus-infected RT4 cells permitted PGE2 signaling as measured by cAMP generation, whereas signaling was suppressed in the 15-PGDH-expressing parental lines, demonstrating that 15-PGDH had a direct impact on PGE2 signaling in cancer cells. Numerous studies have already revealed an important link between elevated levels of PGE2 and tumor development and progression, suggesting there was a potential relationship between PHO and tumors (8, 9, 10). However, up to now, there was only one Slco2a1-mutated patient reported to suffer from colon neoplasm (15). In this study, we reported the first case of HPGD-mutated PHO patient, presenting typical PHO features and atypical soft tissue tumors at bilateral lower legs. It was well known that the effects of PGE2 were mediated via four known receptors EP1, EP2, EP3 and EP4 in individual target cell, involving in cell proliferation, apoptosis and angiogenesis (39). EP-related signaling seemed to play a key role in tumorigenesis. Most recently, via using mPGES1-deficient mice, PTGER4-deficient mice and specific antagonists of EPs, a study from Inada’s laboratory (40) assessing the role of PGE2 in the soft tissue tumors revealed that PGE2 acted on fibroblasts in tumor microenvironment through EP4 receptor. Besides, this research group also demonstrated that tumor growth and vascularization in soft tissues were abrogated by an EP4 receptor antagonist, suggesting PGE2/EP4 signaling played a critical role in the growth of tumors. Unfortunately, since the patient refused tumor biopsies in our department, the in vitro experiment was not available in this study. Whether PGE2/EP4 signaling involved and played a critical role in the tumorigenesis of this PHO patient remained unclear. Notably, radiographic examinations, especially CTA of lower legs, suggested benign soft tissue tumors as there was no increased vascularity and abnormal vascular perfusion found inside the giant tumor (Fig. 2I).

Studies concerning the treatment of PHO patients were limited and no treatment has been shown to reverse the hypertrophic bone changes. Currently, the most commonly used drugs were NSAIDS, since they were effective in alleviating arthritis and easing bone pain. Recently, the novel selective COX-2 inhibitors, etoricoxib, which not only suppress COX-2-derived PGE2 synthesis and lower PGE2 levels from upstream, but also improve biochemical selectivity over that of other selective COX-2 inhibitors (41, 42), has been shown to have a positive therapeutic effect on PHO patients in some clinical studies (21, 23). Indeed, the serum and urinary PGE2 in our patient were decreased after 6-month etoricoxib treatment, confirming its efficacy to treat this disease based on pathogenic considerations. The PHO-related symptoms including joint swelling and hyperhidrosis, as well as the increased biochemical markers including ALP, β-CTX, hsCRP and IL-6 have also been markedly improved within 6 months. These findings were in agreement with the Li and Yuan’s study (21, 23). Interestingly, though the soft tissue tumor persisted, it has not grown since COX-2 inhibitor treatment, indicating the PGE2 might play a central role in tumor progression of PHO patient.

In summary, in the present study, we reported for the first time a Chinese Han PHO patient with soft tissue giant tumors in lower legs. Mutational analysis...
of the patient revealed a common homozygous mutation c.310_311delCT in HPGD gene. In addition to typical clinical features including digital clubbing, periostosis, pachydermia and acro-osteolysis, the patient presented an atypical manifestation, giant soft tissue tumors at both lower legs which have not been reported in HPGD-mutated PHO patient before. After six-month treatment with a novel selective COX-2 inhibitor, etoricoxib (60mg once daily), PGE₂ levels were markedly decreased and PHO-related symptoms such as pachydermia, joint swelling and hyperhidrosis significantly improved in this patient. Though the soft tissue tumors persisted, it seemed to be controlled under the etoricoxib treatment. Further studies and investigations should be performed to reveal the role of PGE₂ signaling on tumorigenesis in PHO.

**References**

1 Uppal S, Diggle CP, Carr IM, Fishwick CW, Ahmed M, Ibrahim GH, Hellwell PS, Latos-Bie lenska A, Phillips SE, Markham A, et al. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. *Nature Genetics* 2008 40 789–793. (https://doi.org/10.1038/ng.153)

2 Sasaki T, Nizeki H, Shimizu A, Shichama A, Hirakiyama A, Okuyama T, Seki A, Kabashima K, Otsuka A, Ishiko A, et al. Identification of mutations in the prostaglandin transporter gene SLC02A1 and its phenotype-genotype correlation in Japanese patients with pachydermoperiostosis. *Journal of Dermatological Science* 2012 68 36–44. (https://doi.org/10.1016/j.jdermsci.2012.07.008)

3 Seifert W, Beninde J, Hoffmann K, Lindner TH, Bassir C, Aksu F, Hubner C, Verbeek NE, Mundlos S, Horn D. HPGD mutations cause cranioosteoarthropathy but not autosomal dominant digital clubbing. *European Journal of Human Genetics* 2009 17 1570–1576. (https://doi.org/10.1038/sj.ejhg.5202049)

4 Diggle CP, Parry DA, Logan CV, Laisse P, Rivera C, Restrepo CM, Fonseca Dj, Morgan JE, Allarey Y, Fontenay M, et al. Prostaglandin transporter mutations cause pachydermoperiostosis with myelofibrosis. *Human Mutation* 2012 33 1175–1181. (https://doi.org/10.1002/humu.22111)

5 Zhang Z, Xia W, He J, Zhang Z, Ke Y, Yue H, Wang C, Zhang H, Gu J, Hu W, et al. Exome sequencing identifies SLC02A1 mutations as a cause of primary hypertrophic osteoarthropathy. *American Journal of Human Genetics* 2012 90 125–132. (https://doi.org/10.1016/j.ajhg.2011.11.019)

6 Zhang Z, He JW, Fu WZ, Zhang QG & Zhang ZL. Mutations in the SLC02A1 gene and primary hypertrophic osteoarthropathy: a clinical and biochemical characterization. *Journal of Clinical Endocrinology and Metabolism* 2013 98 E923–E933. (https://doi.org/10.1210/jc.2012-3568)

7 Seifert W, Kuhnisch J, Tuysuz B, Specker C, Brouwers A & Horn D. Mutations in the prostaglandin transporter encoding gene SLC02A1 cause primary hypertrophic osteoarthropathy and isolated digital clubbing. *Human Mutation* 2012 33 660–664. (https://doi.org/10.1002/humu.22042)

8 Wang D & Dubois RN. Prostaglandins and cancer. *Gut* 2006 55 115–122. (https://doi.org/10.1136/gut.2004.047100)

9 Reader J, Holt D & Fulton A. Prostaglandin E2 EP receptors as therapeutic targets in breast cancer. *Cancer Metastasis Reviews* 2011 30 449–463. (https://doi.org/10.1007/s10555-011-9303-2)

10 Menter DG & Dubois RN. Prostaglandins in cancer cell adhesion, migration, and invasion. *International Journal of Cell Biology* 2012 2012 723419. (https://doi.org/10.1155/2012/723415)

11 Holla VR, Backlund MG, Yang P, Newman RA & Dubois RN. Regulation of prostaglandin transporters in colorectal neoplasia. *Cancer Prevention Research* 2008 1 93–99. (https://doi.org/10.1158/1940-6207.CAPR-07-0009)

12 Markowitz SD. Colorectal neoplasia goes with the flow: prostaglandin transport and termination. *Cancer Prevention Research* 2008 1 77–79. (https://doi.org/10.1158/1940-6207.CAPR-08-0009)

13 Backlund MG, Mann JR, Holla VR, Buchanan FG, Tai HH, Musiek ES, Milne GL, Katkuri S & Dubois RN. 15-Hydroxyprostaglandin dehydrogenase is down-regulated in colorectal cancer. *Journal of Biological Chemistry* 2005 280 3217–3223. (https://doi.org/10.1074/jbc.M411221200)

14 Yan M, Rerko RM, Platter P, Dawson D, Willis J, Tong M, Lawrence E, Lutterbaugh J, Lu S, Willson JK, et al. 15-Hydroxyprostaglandin dehydrogenase, a COX-2 upregulation antagonist, is a TGF-beta-induced suppressor of human gastrointestinal cancers. *PNAS* 2004 101 17468–17473. (https://doi.org/10.1073/pnas.0406142101)

15 Guda K, Fink SP, Milne GL, Molyneaux N, Ravi L, Lewis SM, Dannenberg AJ, Montgomery CG, Zhang S, Willis J, et al. Inactivating mutation in the prostaglandin transporter gene, SLC02A1, associated with familial digital clubbing, colon neoplasia, and NSAID resistance. *Cancer Prevention Research* 2014 7 805–812. (https://doi.org/10.1158/1940-6207.CAPR-14-0108)

16 Li Y, Li S, Sun D, Song L & Liu X. Expression of 15-hydroxyprostaglandin dehydrogenase and cyclooxygenase-2 in non-small cell lung cancer: correlations with angiogenesis and prognosis. *OncoLgy* 2014 8 1589–1594. (https://doi.org/10.18892/ol.2014.2371)

17 Tseng-Rogenski S, Gee J, Ignotoski KW, Kunju LP, Buchert A, Kintner HJ, Morris D, Tallman C, Evron J, Wood CG, et al. Loss of 15-hydroxyprostaglandin dehydrogenase expression contributes to bladder cancer progression. *American Journal of Pathology* 2010 176 1462–1468. (https://doi.org/10.2353/ajpath.2010.090875)

18 Zhang B, Ma X, Li Z, Gao X, Wang F, Liu L, Shen G, Sang Y, Li M, Li Y, et al. Celecoxib enhances the efficacy of 15-hydroxyprostaglandin dehydrogenase gene therapy in treating murine breast cancer. *Journal of Cancer Research and Clinical Oncology* 2013 139 797–807. (https://doi.org/10.1007/s00432-013-1381-9)

19 Erken E, Koroglu Ç, Yildiz F, Özer HT, Gulek B & Tolun A. A novel recessive 15-hydroxyprostaglandin dehydrogenase mutation in a family with primary hypertrophic osteoarthropathy. *Modern
Q Pang et al. PHO patients with soft tissue giant tumor caused by HPGD mutation

Rheumatology 2015 25 315–321. (https://doi.org/10.3109/14937595.2013.874757)

20 Okten A, Mungan I, Kalyoncu M & Orbak Z. Two cases with pachydermoperiostosis and discussion of tamoxifen citrate treatment for arthralgia. Clinical Rheumatology 2007 26 8–11. (https://doi.org/10.1007/s10067-005-1161-2)

21 Li SS, He JW, Fu WZ, Liu YJ, Hu YQ & Zhang ZL. Clinical, biochemical, and genetic features of 41 Han Chinese families with primary hypertrophic osteoarthropathy, and their therapeutic response to etoricoxib: results from a six-month prospective clinical intervention. Journal of Bone and Mineral Research 2017 32 1659–1666. (https://doi.org/10.1002/jbmr.3157)

22 Tuyusz B, Yilmaz S, Kasapcopur O, Ererener-Ercan T, Ceyhun E, Bilguvar K & Gunel M. Primary hypertrophic osteoarthropathy caused by homozygous deletion in HPGD gene in a family: changing clinical and radiological findings with long-term follow-up. Rheumatology International 2014 34 1539–1544. (https://doi.org/10.1007/s00296-014-3037-8)

23 Yuan L, Liao R, Lin Y, Jiang X, Wang Q, Li M, Xing X, Pang Q, Hsieh E & Xia W. Safety and efficacy of cyclooxygenase-inhibition for treatment of primary hypertrophic osteoarthropathy: a single-arm intervention trial. Journal of Orthopaedic Translation 2018 [epub]. (https://doi.org/10.1016/j.jot.2018.10.001)

24 Niesen FH, Schultz L, Jadhav A, Bhatia C, Guo K, Maloney DJ, Pilka ES, Wang M, Oppermann U, Heightman TD, et al. High-affinity inhibitors of human NAD-dependent 15-hydroxyprostaglandin dehydrogenase: mechanisms of inhibition and structure-activity relationships. PLoS ONE 2010 5 e13719. (https://doi.org/10.1371/journal.pone.0013719)

25 Yuan L, Chen L, Liao RX, Lin YY, Jiang Y, Wang O, Li M, Xing XP, Pang QQ, Jiajue R, et al. A common mutation and a novel mutation in the HPGD gene in nine patients with primary hypertrophic osteoarthropathy. Calcified Tissue International 2015 97 336–342. (https://doi.org/10.1007/s00223-015-0024-3)

26 Nomura T, Lu R, Pucci ML & Schuster VL. The two-step model of primary hypertrophic osteoarthropathy: ultrasound and MRI findings. Pediatric Radiology 2016 46 727–730. (https://doi.org/10.1007/s00247-016-3544-8)

27 Giannace G, Diggle CP, Legger EG, Tekstra J, Prakken B, Brenkman AB, Carr IM, Markham AE, Bonthron DT & Wulfraat N. Primary hypertrophic osteoarthropathy: an update on patient features and treatment. Journal of Rheumatology 2015 42 2211–2214. (https://doi.org/10.3899/jrheum.150364)

28 Adams B, Amin T, Leone V, Wood M & Kraft JK. Primary hypertrophic osteoarthropathy: ultrasound and MRI findings. Lancet 2015 385 336–342. (https://doi.org/10.1016/S0140-6736(14)6071–6073)

29 Sugimoto Y & Narumiya S. Prostaglandin E receptors. Biochemical Society Transactions 2001 29 11613–11617. (https://doi.org/10.1042/bst03611613)

30 Jajic Z, Jajic I & Nemcic T. Primary hypertrophic osteoarthropathy: clinical, radiologic, and scintigraphic characteristics. Archives of Clinical Radiology 2001 32 136–142. (https://doi.org/10.1016/S1098-4409(01)00251-X)

31 Calabrese O, Rittinger O, Punaro MG, Markham AE, et al. Common and recurrent HPGD mutations in Caucasian individuals with primary hypertrophic osteoarthropathy. Rheumatology 2010 49 1056–1062. (https://doi.org/10.1093/rheumatology/kerq48)

32 Javic Z, Javic I & Nemcic T. Primary hypertrophic osteoarthropathy: clinical, radiologic, and scintigraphic characteristics. Archives of Clinical Radiology 2001 32 136–142. (https://doi.org/10.1016/S1098-4409(01)00251-X)

33 Pineda C. Diagnostic imaging in hypertrophic osteoarthropathy. Clinical and Experimental Rheumatology 1992 10 Supplement 1 27–33.

34 Sugiimoto Y & Narumiya S. Prostaglandin E receptors. Journal of Biological Chemistry 2007 282 11613–11617. (https://doi.org/10.1074/jbc.R600038200)

35 Inada M, Takita M, Yokoyama S, Watanabe K, Tominari T, Matsutomo C, Hiraiz M, Maru Y, Maruyama T, Sugiimoto Y, et al. Direct melanoma cell contact induces stromal cell autocrine prostaglandin E2-E4 receptor signaling that drives tumor growth, angiogenesis, and metastasis. Journal of Biological Chemistry 2015 290 29781–29793. (https://doi.org/10.1074/jbc.M115.669481)

36 Cho H, Walker A, Williams J & Hasty KA. Study of osteoarthritic treatment with anti-inflammatory drugs: cyclooxygenase-2 inhibitor and steroids. BioMed Research International 2015 2015 595273. (https://doi.org/10.1155/2015/595273)

Received in final form 14 April 2019
Accepted 7 May 2019
Accepted Preprint published online 7 May 2019