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Original Article

Type II primary hypertrophic osteoarthropathy pedigree: a case report and review of the literature

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Abstract: Primary hypertrophic osteoarthropathy (PHO) is a rare disease that is characterized by benign hyperplasia of long bones and digital clubbing. Solute carrier organic anion transporter family member 2A1 (*SCLA2A1*) gene was recently discovered to be one of the pathogenic genes of PHO, resulting in a relatively latent onset type of the disease. Here we present a 19-year-old male patient, whose major complaint was 3-year history of clubbing of fingers and toes. The elder brother of the patient experienced similar symptoms at the same age, and relieved without treatment at the age of 26. The search for a secondary cause of hypertrophic osteoarthropathy remained negative. Genetic examination confirmed a heterozygous mutation on *SCLA2A1* gene, indicating the diagnosis of PHO.

Keywords: Primary hypertrophic osteoartropathy, *SCLA2A1* gene, genetic examination

Background

Hypertrophic osteoarthropathy (HO) is a rare disease that is characterized by digital clubbing, periostosis, and pachydermia [1]. The disease is classified as primary or secondary. Secondary HO is mostly related to malignancy or other underlying causes including inflammatory bowel disease, congenital heart disease, pulmonary fibrosis and liver cirrhosis. Primary HO is also called pachydermoperiostosis, which was first scientifically described in 1868 by Friedreich in two affected brothers with periostosis [2]. The inheritance mode of PHO has previously been confirmed to be autosomal dominant with incomplete penetrance or recessive inheritance [3, 4].

Recent studies have divided primary HO into two types based on different genetic mutations. In 2008, Uppal et al. discovered that homozygous mutations in hydroxyprostaglandin dehydrogenase (*HPGD*) gene were the cause of PHO [5]. *HPGD* gene encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), and the mutation of *HPGD* gene results in the inactivation of 15-PGDH and the accumulation of prostaglandin E2. The increased level of prostaglandin E2 contributes to regional chronic inflammatory reaction and symptoms of digital clubbing etc.. Recently, Zhang et al. revealed that *SLCO2A1* was another pathogenic gene of PHO [6]. *SLCO2A1* encodes the prostaglandin transporter (PGT), and is also related to prostaglandin E2 (PGE2) degradation.

Herein, we present a case of a 19 year-old Chinese patient with PHO who had characteristic symptoms of type II primary HO with *SLCO2A1* gene mutation.

Case presentation

A 19-year-old Chinese man complained of pan-digital clubbing and joint pain for three years, along with thickened facial skin and acne in face and back. He also experienced palmar and plantar hyperhidrosis and joint pain in bilateral knees and wrists. He had no history of congenital heart disease, pulmonary disease, gastrointestinal disease, or malignancy. His elder brother experienced a similar condition at the age of sixteen, and the symptoms relieved spontaneously after his twenty-six years of age without any confirmed diagnosis.

Physical examination showed stable vital signs. His body height was 170 cm and body weight was 53 kg. He had pan-digital clubbing, thick-

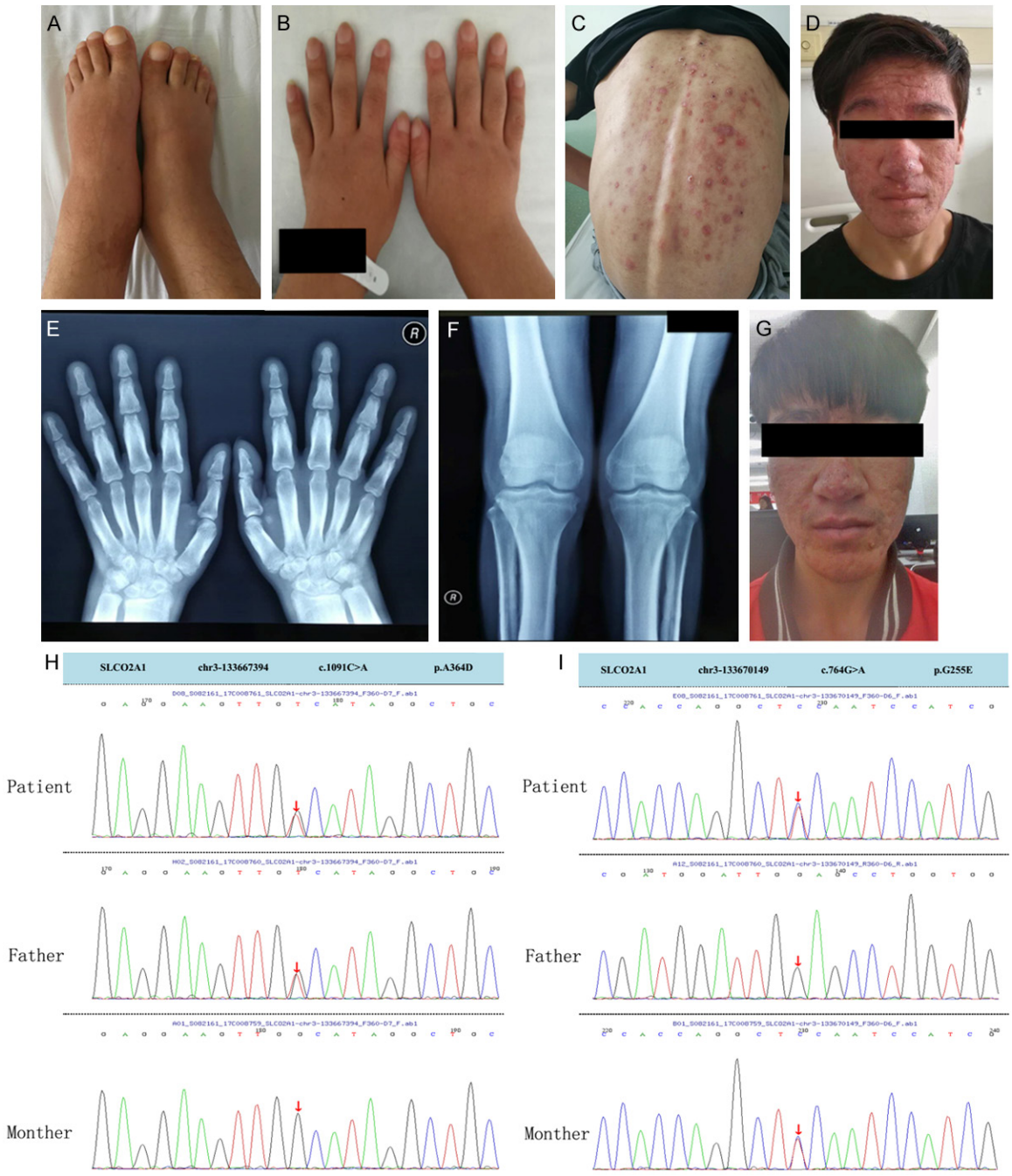

Figure 1. Physical examination, X-rays, and genetic examination results of the patient. A. Digital clubbing of feet. B. Digital clubbing of hands. C. Back skin hyperplasia and acne. D. Hyperplasia and acne in face. E. X-ray showing periostosis in bilateral wrists. F. X-ray showing periostosis in bilateral femur, tibia and fibula, and an increase in soft tissue content. G. The skin change was relieved after the patient was put on celecoxib for one year. H and I. The genetic examinations of the patient and his parents showing two compound heterozygous missense mutations in *SLCO2A1*.

ened facial skin, facial acne, and back skin, as well as diffused swelling of hands and feet with watch-glass nails (**Figure 1A-D**). Cardiopulmonary and abdominal examinations were normal.

Laboratory reports indicated that total leucocyte count was 8500/mm^3 (normal 4000-11000), hemoglobin 133 g/l (120-150). Serum electrolytes, liver and renal function tests were all within normal ranges. His erythrocyte sedi-

mentation rate (ESR) was 40 mm in the first hour. C reactive protein (CRP) was 80.60 mg/L (normal < 8 mg/L). Rheumatoid factor and autoimmune antibodies were negative.

X-ray revealed periostosis in bilateral femur, tibia and fibula, and in bilateral wrists (**Figure 1E**, **1F**). Joint ultrasounds showed effusion in bilateral knees and ankles.

Secondary causes of HO were ruled out due to a normal chest X-ray, echocardiogram, and tumor biomarkers. A differential diagnosis of acromegaly was excluded since his IGF-1 was normal and growth hormone (GH) levels were within normal range (< 1.0 ng/ml) during the oral glucose suppression test.

SLCO2A1 gene examination revealed two compound heterozygous missense mutations (c.764G > A and c.1091C > A) (**Figure 1H**, **1I**). However, the elder brother of the patient experienced similar symptoms during puberty but refused a genetic examination. After confirming the diagnosis of PHO, the patient was put on celecoxib 200 mg twice a day. Joint pain and acne were relieved soon after medication. The patient was under regular follow-up for one year, and thickened skin and periostosis were significantly reversed (**Figure 1G**).

Discussion and learning points

Hypertrophic osteoarthropathy (HO) is poorly recognized since it is a rare disease. There is still a lack of data for the prevalence of PHO. Among all cases of hypertrophic osteoarthropathy, only 5% of them are PHO. It is also called Touraine-Solente-Gole syndrome. The syndrome occurs in males predominantly, and the sex ratio is 9:1. Martinez-Lavin et al. reviewed 125 cases of PHO, and demonstrated that 89% of them were male and 38% had a familial transmission history [7]. Female PHO patients have relatively mild symptoms.

The clinical manifestations of PHO involve digital clubbing, periostitis of bones, and hyperplasia of skin. Typical cutaneous alterations are sebaceous gland abnormality (e.g. acne, seborrheic dermatitis, and hyperhidrosis) and soft tissue hyperplasia (e.g. clubbing of fingers). In PHO cases, it was reported that 100% of patients had clubbing of fingers, 85.5% hyperhidrosis, 68.4% skin hyperplasia in lower extremity, and 76% joint alternation [8]. In this case, typical hyperplasia of skin and severe acne in facial area and back was seen since the puberty of the patient, which was in accordance with previous studies.

In our case, the patient had joint pain in lower extremities, and joint ultrasounds showed effusion in bilateral knees and ankles. Knees are the most common affected joints in PHO patients, along with ankles and small joints in hands. X-ray plays a critical role in the diagnosis of PHO, which presents as symmetric periostosis in long bones. Osteolysis is noticed in patients with PHO history over ten years [9]. In this case, symmetric pariostosis was discovered in bilateral femur, tibia, and fibula, which provided evidence to the diagnosis of PHO. The effusion fluid in joints is not inflammatory, thus arthrocentesis and synovium biopsy is not recommended in the diagnosis of PHO.

A most differential diagnosis is to rule out secondary hypertrophic osteoarthropathy. Secondary HO is similar with the primary one in clinical features and imaging, but secondary type has no family history and is latent onset compared with PHO. Also, a cause of secondary HO could be discovered, including malignancy, congenital heart disease, and gastroenteropathy.

PHO is a hereditary disease, and the familial transmission pattern is in line with autosomal dominant with incomplete penetrance or recessive inheritance. The underlying mechanism of PHO is the genetic alteration in the prostaglandin metabolic pathway. Homozygous mutations in *HPGD* were revealed to be a cause of PHO. In 2013, homozygous mutations in solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) were found as another cause of PHO. Both genes are involved in PGE2 degradation. Metabolic clearance of PGE2 consists of a selective carrier-mediated uptake across the plasma membrane by *SLCO2A1* and degradation by HPGD inside the cell [10]. The elevated level of PGE2 due to the failure of degradation causes the pathogenesis of PHO [11]. Therefore, PHO are divided into two categories according to different molecular alternation: hypertrophic osteoarthropathy, primary, autosomal recessive 1 (PHOAR1) resulted by HPGD deficiency; and hypertrophic osteoarthropathy, primary, autosomal recessive 2 (PHOAR2) resulted by *SLCO2A1* deficiency.

PHOAR1 and PHOAR2 differ not only in genetic alternations, but also in age of onset and severity. Our case presented symptoms of typical PHOAR2 with *SLCO2A1* deficiency. In general, the age of onset has a bimodal distribution, and the peak age is one year old for PHOAR1 and fifteen years old for PHOAR2 [8]. In terms of clinical manifestations, the age of onset is during puberty in PHOAR2, while the peak age is at one year old in PHOAR1 [12]. The sex ratio is significantly distinct from each other. In PHOAR1 patients, the male to female ratio is close to 1:1, while almost all patients of PHOAR2 are male. Additionally, congenital abnormality (e.g. cranial suture defects, patent ductus arteriousus) is more prevalent in PHOAR1 patients, and myelofibrosis induced anemia is found notably in PHOAR2 patients [13]. Recent study observed age-related reduction of urinary PGE2 and PGE-M in PHOAR2 patients, which could be applied in clinical practice for the differential diagnosis of the two types of PHO, other than genetic analysis [14]. In our case, urinary PGE2 was unable to evaluate, and we are planning to collect the urine sample of the patient for urinary PGE2 test in follow-ups for confirmation of the two types of PHO.

In terms of previous study, the familial transmission pattern of PHOAR2 is autosomal recessive mode. However, in our case, the patient had two compound heterozygous missense mutations (c.764G > A and c.1091C > A) in *SLCO2A1* gene, and both of the mutations have not been reported before. This phenomenon is hard to explain in case of the missing data of *SLCO2A1* gene in other families of the pedigree. A similar condition was reported in 2013 by Zhang et al., where two patients were found to carry a heterozygous mutation, and other relatives who carried the same mutation did not present with PHO symptoms [14]. Several novel mutations of *SLCO2A1* gene were discovered in PHO patients of Chinese and Japanese decent after Zhang et al. reported the common missense mutation (c.940 + 1G > A) [15, 16]. A smaller number of patients with *SLCO2A1* gene mutation were from Africa or Europe [17, 18]. In our case, the missense mutation of c.764G > A was reported in previous study of Zhang et al. However, the *SLCO2A1* mutation of c.1091C > A has not yet been seen in reported cases, and could be confirmed as a novel missense mutation of *SLCO2A1* for PHO if the patient's brother's genetic examination was performed. In the differential diagnosis of PHO, the measurement of urinary PGE2 and PGE-M levels could provide evidence for this situation rather than serum PGE2 level [15].

Most of PHOAR2 cases are self-remission with symptoms that are more active in juvenile age and puberty. When patients with PHOAR2 enter adult age, the disease become asymptomatic. Therefore, management of PHOAR2 aims to relieve the symptoms until the state of illness remains stable. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended for arthralgia. Glucocorticoids and tamoxifen are also possible choices for arthritis due to PHO. Diphosphonates could be applied in osteoporosis secondary to PHO. In our case, the patient was put on celecoxib 200 mg twice a day and alendronate sodium 70 mg per week, and his joint pain was remarkably relieved.

In conclusion, we report a male patient with PHO due to the genetic mutation in *SLCO2A1* gene. Some of the clinical features of PHOAR2 are distinct from PHOAR1, including the age of onset, accompanying conditions, and sex category of patients. In clinical practice, above symptoms, genetic examinations are available choice for different categories of PHO. NSAIDs could be used for arthralgia since the disease is self-remission.

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Disclosure of conflict of interest

None.

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