**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 58819

**Manuscript Type:** CASE REPORT

**Discontinuous polyostotic fibrous dysplasia with multiple systemic disorders and unique genetic mutations: A case report**

Lin T *et al*. PFD with unique genetic mutations

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**Author contributions:** Shen JN, Lin T, and Yin JQ contributed to conceptualization; Lin T, Zou CY, Liu WW, Li XY, Lin JF, Zhang XX, and Zhao SQ contributed to investigation; Lin T and Li XY contributed to writing the original draft; Lin T, Liu WW, Li XY, Lin JF, Zhang XX, Zhao SQ, Zou CY, Xie XB, and Huang G contributed to writing, reviewing, and editing the article; All authors approved the final manuscript.

**Supported by** National Natural Science Foundation of China, No. 81703017; The Science and Technology Projects of Guangzhou, China, No. 201804010080.

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**Received:** August 25, 2020

**Revised:** September 27, 2020

**Accepted:** October 26, 2020

**Published online:**

**Abstract**

BACKGROUND

Polyostotic fibrous dysplasia (PFD) is an uncommon developmental bone disease in which normal bone and marrow are replaced by pseudotumoral tissue. The etiology of PFD is unclear, but it is generally thought to be caused by sporadic, post-zygotic mutations in the *GNAS* gene. Herein, we report the case of a young female with bone pain and lesions consistent with PFD, unique physical findings, and gene mutations.

CASE SUMMARY

A 27-year-old female presented with unbearable bone pain in her left foot for 4 years. Multiple bone lesions were detected by radiographic examinations, and a diagnosis of PFD was made after a biopsy of her left calcaneus with symptoms including pre-axial polydactyly on her left hand and severe ophthalmological problems such as high myopia, vitreous opacity, and choroidal atrophy. Her serum cortisol level was high, consistent with Cushing syndrome. Due to consanguineous marriage of her grandparents, boosted whole exome screening was performed to identify gene mutations. The results revealed mutations in *HSPG2* and *RIMS1*, which may be contributing factors to her unique findings.

CONCLUSION

The unique findings in this patient with PFD may be related to mutations in the *HSPG2* and *RIMS1* genes.

**Key Words:** Polyostotic fibrous dysplasia; Genetic mutation; Hypercortisolism; Drug resistance; Ophthalmological problems; Case report

Lin T, Li XY, Zou CY, Liu WW, Lin JF, Zhang XX, Zhao SQ, Xie XB, Huang G, Yin JQ, Shen JN. Discontinuous polyostotic fibrous dysplasia with multiple systemic disorders and unique genetic mutations: A case report. *World J Clin Cases* 2020; In press

**Core Tip:** Polyostotic fibrous dysplasia is an uncommon developmental bone disease. It mostly presents as progressive fibrous dysplasia with decreased skeletal strength and increased bone pain. Herein, we report the case of a 27-year-old female suffering multiple-sites bone pain on the left ischium, fibula, talus, and calcaneus with extreme high serum cortisol level, which might explain her Cushing syndrome. Preaxial polydactyly on her left hand and severe ophthalmological problems were also found in this patient. Boosted whole exome screening revealed unique gene mutations in *HSPG2* and *RIMS1* that may contribute to her symptoms.

**INTRODUCTION**

Fibrous dysplasia (FD) is a genetic neoplastic bone disorder where normal bone and marrow are replaced by osteofibrous connective tissue, leading to bone pain, deformity, and fractures[1]. While the condition is benign, surgery is necessary to alleviate pain and repair or stabilize the affected bones. FD accounts for approximately 7% of all benign tumor-like bone lesions[2]. There are three defined subtypes of FD: (1) Monostotic; (2) Polyostotic fibrous dysplasia (PFD); and (3) McCune Albright syndrome (MAS). Among these, monostotic is the most common (70%), while PFD and MAS are relatively rare[3].

Bisphosphonates are the primary medical treatment for FD. Although a 1994 study showed that intravenous pamidronate (60 mg per day over 3 d, every 6 mo) can result in the refilling of bone lesions and cortical thickening of some patients with FD, its effectiveness in controlling disease progression remains uncertain[4]. Drugs such as denosumab have been reported to be effective in reducing bone pain and slowing the lesion growth rate in patients with receptor activator of nuclear factor kappa-B ligand expression, however, its use is debatable when the side effects are considered in light of the therapeutic effects[1]. Other treatments include surgery, physical rehabilitation, and long-term conservative management and close monitoring[5]. As such, to develop better treatments for FD, a better understanding of the genetic and molecular mechanisms of FD is needed.

FD is generally thought to be caused by sporadic, post-zygotic mutations in the *GNAS* gene, located on chromosome 20q13.3, which result in the activation of the signaling transduction pathway that generates cyclic adenosine monophosphate[6].

Herein, we report the case of a 27-year-old Chinese woman diagnosed as PFD with multiple discontinuous lesions, Cushing syndrome, and ophthalmological disorders. She was unresponsive to bisphosphonate treatment, and gene sequencing revealed mutations in the *HSPG2* and *RIMS1* genes.

**CASE PRESENTATION**

***Chief complaints***

The patient complained of increasing pain in her left foot and difficulty walking over the past 4 years.

***History of present illness***

Over a 4-year period, she experienced increasing pain in her left foot and difficulty walking. Radiographic examinations at local hospitals suggested a diagnosis of PFD, which was confirmed by a biopsy of her left calcaneus.

***History of past illness***

The patient had a history of frequent bone fractures since birth. She also presented with typical symptoms of Cushing syndrome and ophthalmological disorders including high myopia, vitreous opacity, and choroid atrophy. Hypothalamic amenorrhea and irregular menstruation were also present.

***Personal and family history***

The patient’s maternal grandparents were consanguineous (cousins).

***Physical examination***

The patient experienced pain on palpation of her left foot. No obvious swelling was observed, and the foot was neurovascularly intact. Signs of Cushing syndrome included abdominal obesity with thin arms and legs, acne, a round face, and a fat lump between the shoulders (Figure 1A-C)[7]. Her teeth were noted to be poorly developed (Figure 1D), and she had thumb duplication on her left hand (Figure 1E and F).

***Laboratory examinations***

Her serum calcium and phosphate levels were normal as well as the levels of hormones that regulate calcium metabolism, including parathyroid hormone, 25-hydroxy vitamin D, and osteocalcin. Her serum cortisol level was 1492.00 nmol/L, which was extremely high (reference range of 147.30-609.30 nmol/L), and her triglyceride and uric acid levels were also elevated (Table 1).

***Imaging examinations***

Skeletal scintigraphy showed multiple bone lesions on her left ischium, distal fibula, calcaneus, and talus (Figure 2A and B). Computed tomography (CT) revealed well-circumscribed bone lucencies and ground-glass opacities in the calcaneus and talus (Figure 2C and D). No evidence of pituitary or adrenal lesions was identified on brain computed tomography.

**FINAL DIAGNOSIS**

Based on the patient’s clinical symptoms, imaging studies, and biopsy results (Figure 3), a diagnosis of PFD was made after consultations with musculoskeletal oncologists, radiologists, and pathologists. Her other symptoms and signs were considered likely to be caused by her unique genetic mutations.

**TREATMENT**

In 2016, the patient began intravenous zoledronic acid every 6 mo and received four doses, followed by sodium pamidronate every 3 mo and received three doses. She was then continued on oral alendronate weekly.

**OUTCOME AND FOLLOW-UP**

After evaluating the risk and expenses of surgery, the patient chose to continue bisphosphonate treatment with regular monitoring of disease progression. Over a 2-year period, the size of the lesions did not become markedly larger. However, dual-energy X-ray absorptiometry indicated a new lower bone mass in the proximal femur and the distal fibula as compared to an examination 2 years prior, suggesting possible disease progression. The treatments, however, did not alleviate the pain in her left foot, indicating resistance to the anti-bone resorption treatments. Nonsteroidal anti-inflammatory drugs were prescribed for her left foot bone pain.

**DISCUSSION**

Herein, we presented the case of a young woman with PFD combined with multiple systemic disorders and resistance to bisphosphonate treatment. PFD was confirmed by biopsy of her left calcaneus. However, her additional symptoms were markedly different from most patients with PFD.

We reviewed 6 cases of PFD identified in our search of the literature[2,8-12], and the details of the 6 cases along with the details of our case are summarized in Table 2. In patients with PFD, when lesions involve the orbital region the primary findings are facial asymmetry, orbital dystopia, and orbital proptosis[13], none of which were identified in our patient. Therefore, it is likely that the ophthalmological disorders of our patient are not related to her PFD, but rather to other genetic defects.

Some of the patients with PFD/MAS in our review did have multiple bone lesions and endocrine disorders (*e.g.*, precocious puberty, hypercortisolism, and hyperthyroidism) and skin pigmentation (“café-au-lait” spots). Hypercortisolism was the rarest symptom associated with PFD/MAS and is reported to occur exclusively in newborns[14]. However, our patient had an extremely high serum cortisol level, a finding not reported in the cases we reviewed.

PFD is difficult to treat or cure because of multiple advanced bone lesions and genetic defects of the osteoprogenitors. Studies have shown that radiographic findings and bone pain are improved in approximately 50% patients treated with bisphosphonates[15-17]. However, neither oral nor intravenous bisphosphonates were effective in our patient. Curettage is indicated to alleviate bone pain and improve limb function; however, our patient declined any surgical treatment.

Since multiple gene mutations were identified by boosted whole exome screening in our patient, we hypothesize that her unique symptoms are likely due to the gene mutations (Table 3). Notably, the missense and non-sense point mutations in *RIMS1* and *HSPG2* are likely responsible for her unique symptoms (Figure 4), because mutations in these two genes are reported to be associated with bone and ocular diseases, respectively.

Analysis of the genetic sequencing results of the patient and her parents indicated that the patient’s mutations were mostly heterozygous and similar to those of her mother. This indicates that the mutated genes came from her mother, whose parents had a consanguineous marriage. Surprisingly, the *HSPG2* mutation was homozygous, which is likely due to uniparental disomy[18] [a single chromosome from her mother was duplicated leading to the homozygous mutation in *HSPG2* (Figure 5)].

*HSPG2* is an essential, highly conserved gene widely expressed throughout the development of cartilage and the formation and calcification of skeletal bone[19]. Mutations in *HSPG2* can lead to two autosomal recessive inheritance skeletal disorders; Schwartz-Jampel syndrome (Online Mendelian Inheritance in Man 255800) and dys-segmental dysplasia, Silverman-Handmaker type (Online Mendelian Inheritance in Man 224410)[20]. Dys-segmental dysplasia, Silverman-Handmaker type can result in severe cartilage matrix anomalies, and even neonatal death, whereas patients with Schwartz-Jampel syndrome may have chondrodysplasias, myotonic myopathy, and facial and ocular abnormalities. Heterozygous mutations in *RIMS1* mainly cause cone-rod dystrophy, which is characterized by reduced photophobia, central vision, and reduced color vision[21].

We did not identify mutations in *GNAS* in any of the blood samples we tested, although mutations in *GNAS* have been reported to be associated with PFD. It is generally thought that mutations in *GNAS* occur early in embryogenesis, and cells with defects are distributed in different tissues of the body as a result of embryonic cell migration[22]. To determine if *GNAS* mutations are present in our patient, bone lesion tissue samples require further sequencing analysis or molecular testing.

**CONCLUSION**

Herein, we presented the case of a patient with PFD with the unique findings of pre-axial polydactyly, Cushing syndrome, ophthalmological abnormalities, and resistance to bisphosphonate treatment. Gene sequencing revealed mutations in *HSPG2* and *RIMS1*, which may be responsible for her unique findings.

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**Footnotes**

**Informed consent statement:** Informed consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Manuscript source:** Unsolicited manuscript

**Peer-review started:** August 9, 2020

**First decision:** September 12, 2020

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ruiz MA **S-Editor:** Huang P **L-Editor:** Filipodia **P-Editor:**

**Figure Legends**



**Figure 1** **Photographic images of the patient showing signs of Cushing syndrome**. A-C: Abdominal obesity with thin arms and legs, acne, a round face and a fat lump between the shoulders (black arrows); D: Poorly developed teeth; E and F: Thumb duplication on the left hand (black arrow).



**Figure 2 Radiography examination results.** A: Anterior view; B: Posterior view of skeletal scintigraphy showing the location of the bone lesions on left ischium and left fibula, talus, and calcaneus (black arrows); C and D: Computed tomography shows well-circumscribed bone lucencies and ground-glass opacities in left talus and calcaneus (yellow arrows).



**Figure 3** **Pathological reports**. A: Fibrous and osseous tissue are present in varying proportions [hematoxylin-eosin (HE), 40 ×]. The box shows the view field of B; B: The fibrous tissue is composed principally of bland fibroblastic cells. Mitoses are uncommon (HE, 100 ×). The box shows the view field of C; C: The osseous component is comprised of irregular, curvilinear, trabeculae of woven or rarely lamellar woven bone (HE; 200 ×).



**Figure 4** **Sequencing chromatograms of the analyzed genes.** A: Results for *HSPG2*; B: Results for *RIMS1*. The red arrows indicate the variants in *HSPG2* (c.6913G>A, p.Asp2305Asn) and *RIMS1* (c.3139del, p.Thr1047His). The variants indicate a maternal source.



**Figure 5** **Possible genetic pedigree: The inheritance of *HSPG2* and *RIMS1*.** The *HSPG2* mutation is homozygous, while the *RIMS1* mutation is heterozygous. The abnormal genotype of *HSPG2* is likely caused by uniparental disomy, a single chromosome from her mother is duplicated leading to the homozygous mutation in *HSPG2*.

**Table 1 Laboratory tests**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Unit** | **Reference** | **Result** |
| Parathyroid hormone | pg/mL | 15.3-68.3 | 23.7 |
| 25-OH-VitD | nmol/L | 47.7-144 | 121.40 |
| Osteocalcin | ng/mL | Male, 9.80-26.40; Female, 7.70-21.70 | 7.05 |
| Calcium | mmol/L | 2.08-2.80 | 2.61 |
| Serum phosphate | mmol/L | 1.00-1.94 | 1.61 |
| Cortisol, 8:00-10:00 | nmol/L | 147.3-609.3 | 1492.00 |
| Triglyceride | mmol/L | < 1.70 | 1.88 |
| Uric acid | mmol/L | 150-360 | 689 |
| Bone specific alkaline phosphatase | mg/L | 11.4-24.0 | 15.86 |
| Hematocrit | % | Male, 41-53; Female, 36-46 | 47.80 |
| Eosinophils | % | 1-3 | 8.10 |

25-OH-VitD: 25-Hydroxy vitamin D.

**Table 2 Cases diagnosed as polyostotic fibrous dysplasia**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Sex** | **Age** | **Location** | **Appendix** | **Treatment** | **Outcome** |
| Sagmeister *et al*[12] | 2016 | F | 27 | Throughout the skeleton. Transverse fracture of the distal right femur | Continuous lesions, extensive bone expansion, cyst formation, cortical loss | Skin traction for 8 wk. Intensive physiotherapy for the fracture | Recovered well, returning to baseline 3 mo later |
| Wu *et al*[2] | 2014 | F | 38 | Sternum, thoracic spine, ribs, right femur, and tibia | Multiple lytic, expansile lesions, continuous pathologic fractures in the thoracic spine | Surgical therapy. Diphosphate therapy with Vit D and calcium | Completely recovered. Able to participate in daily life and work 2 yr later |
| Kodama *et al*[10] | 2012 | F | 8 | Right pelvis, bilateral femurs, and fibula | Discontinuous lesions | Thigh coxa valga osteotomy and plate fixation. Diphosphate therapy | No complaints of severe pain in lower extremity. Low bone turn-over rate |
| Aras *et al*[9] | 2012 | M | 48 | Cranium, left hemithorax, bilateral upper, lower extremities, and pelvic bones | Continuous lesions, bladder cancer | No treatment reported | No outcome reported |
| Boston *et al*[8] | 1994 | M | 3.3 | Proximal left femur and proximal left humerus | Albright-McCune syndrome, no café-au-lait pigmentation, Cushing syndrome | Bilateral adrenalectomy at 7-yr-old with steroid replacement | Cushing syndrome removed. Still with prepubertal and elevated liver enzyme |
| Lourenço *et al*[11] | 2015 | F | 17 d | Multiple lesions with fracture in left ulna | Multiple organs involved, Café-au-lait pigmentation, mosaic *GNAS* gene mutation | Metyrapone therapy for Cushing syndrome | Cushing syndrome recovered. Death due to respiratory infection |
| The current case |  | F | 27 | Left ischium, left distal fibula, calcaneus, and talus | Discontinuous lesions, intractable bone pain, Cushing syndrome | Diphosphate therapy | Still severe pain. Difficulty participating in daily life and job |

M: Male; F: Female.

**Table 3 Result of the boosted whole exome screening**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene** | **Function of the protein coded** | **Mutation** | **Source** | **Associated disease** |
| *RIMS1* | A *RAS* gene superfamily member that regulates synaptic vesicle exocytosis | Point mutation Thr1047His | Maternal, heterozygous | Cone-rod dystrophy type 7 |
| *HSPG2* | Perlecan that is found in the extracellular matrix | Point mutation Asp2305Asn | Maternal, homozygous | S-J syndrome type 1 |
| *APC* | Negative regulator of β-catenin/Wnt pathway | Point mutation Lys1586Met | Maternal, heterozygous | Colorectal cancer associated with FAP |
| *BGN* | A member of the SLRP family | Point mutation p.Asp168Glu | Maternal, heterozygous | SPD X-linked MLS |
| *BMPR1B* | Transmembrane serine/threonine kinases involving TGF-β pathway | Point mutation Met301Val | Maternal, heterozygous | Pulmonary arterial hypertension |
| *CC2D2A* | Play a critical role in cilia formation | Point mutation Gly317Arg | Maternal, heterozygous | Meckel syndrome type 6. Joubert syndrome type 9 |
| *CDH23* | Cadherin superfamily involved in stereocilia organization and hair bundle formation | Point mutation Asp168Glu | Spontaneous, heterozygous | Breast cancer |
| *CHD7* | Protein that contains several helicase family domains | Point mutation Asp1486Gly | Spontaneous, heterozygous | CHARGE syndrome |
| *FLNA* | An actin-binding protein that crosslinks actin filaments and links actin filaments to membrane glycoproteins | Point mutation Asp1314Asn | Maternal, heterozygous | Several syndromes including PNH, OPDS, FMD and so on |
| *CILK1* | Eukaryotic protein kinases | Point mutation Val215Met | Maternal, homozygous | ECD |

ECD: Endocrine-cerebroosteo-dysplasia; FAP: Family adenous polyps; FMD: Frontometaphyseal dysplasia; MLS: Meester-Loeys syndrome; OPDS: Otopalatodigital syndromes; PNH: Periventricular nodular heterotopias; SJS: Schwartz-Jampel syndrome; SLRP: Small leucine-rich proteoglycan; SPD: Spondyloepimetaphyseal dysplasia; TGF-β: Transforming growth factor beta.