OLGU SUNUMU CASE REPORT

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Differential Diagnosis of Juvenile Arthritis: A Rare Disease with Hypertrophic Osteoarthropathy

Jüvenil Artritin Ayırıcı Tanısı: Hipertrofik Osteoartropati Görülen Nadir Bir Hastalık

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ABSTRACT Pachydermoperiostosis is a rare disease characterized by clubbing, periostosis, and soft tissue swelling, caused by mutations in any of the genes involved in prostaglandin metabolism (*SCLO2A1 and HPDG*). Disease may also cause inflammatory arthritis and included in the differential diagnosis of juvenile chronic arthritis. A 17-year-old boy presented to our pediatric rheumatology outpatient clinic with the complaints of pain and swelling in bilateral knees and ankles that has been present for one year but got worsened in the last month. On physical examination he had rough face with furrowing of skin on face and scalp, and clubbing on all digits. A homozygote mutation detected on *SLCO2A1* gene and patient was diagnosed as primary complete pachydermoperiostosis. Herein, we presented a pediatric case with inflammatory arthritis, diagnosed as pachydermoperiostosis based on clinical and radiological findings.

Keywords: Arthritis; pachydermoperiostosis; rare diseases

ÖZET Pakidermoperiostozis, prostaglandin metabolizmasında yer alan genlerin (*SCLO2A1 ve HPDG*) herhangi birindeki mutasyon sonucu meydana gelen, çomak parmak, periostoz ve yumuşak doku hiperplazisi ile karakterize nadir bir hastalıktır. Hastalık inflamatuar artrite sebep olabilmekte ve jüvenil kronik artritin ayırıcı tanısında yer almaktadır. On yedi yaşında erkek hasta, 1 yıldır olan ama son 1 aydır kötüleşen, her iki diz ve ayak bileklerinde ağrı ve şişlik yakınmasıyla çocuk romatolojisi polikliniğine başvurdu. Fizik muayenesinde artrit dışında her iki el parmaklarında çomaklaşma, yüz ve saçlı deride artmış katlantılar ve kaba yüz görünümü vardı. Primer komplet pakidermoperiostozis düşünülen hastanın *SLCO2A1* geninde homozigot mutasyonu saptandı. İnflamatuar artrit ile başvurup klinik ve radyolojik bulgular ile primer hipertrofik osteoartropati tanısı alan pediatrik bir olgu sunduk.

Anahtar Kelimeler: Artrit; pakidermoperiostozis; nadir hastalıklar

Hypertrophic osteoarthropathy (HOA) can be seen either as primary and secondary. Secondary form, also called pulmonary HOA, could be associated with underlying cardiopulmonary diseases and malignancies.[1] Primary form, pachydermoperiostosis (PDP), also known as primary HOA, accounts 3-5% of cases.[2]

PDP, is a rare genetic disease, arises from the mutations of genes (*HPGD* and *SLCO2A1*) involved in prostaglandin metabolism.[3,4] It is characterized by digital clubbing, soft tissue hyperplasia, and periostosis.[5] Genetic transmission may be either autosomal recessive or dominant and phenotype of the disease may be classified as complete, incomplete or fruste forms.[6] Herein, we presented a pediatric case with inflammatory arthritis, diagnosed as primary complete PDP based on the clinical and radiological findings.

CASE REPORT

A 17-year-old boy patient was referred to the pediatric rheumatology outpatient clinic for evaluation of pain and swelling in both knees and ankles. His complaints were present for a year but got worsened in the last month and were accompanied by morning stiffness lasting one to three hours. He had no fever, diarrhea, abdominal pain and rash. Intermittently iron

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supplementation for iron deficiency anemia was employed since he was 11-year-old. Because of the non-responsive anemia, he was evaluated by pediatric gastroenterology four years ago. Endoscopic examination revealed nodularity on duodenal mucosa, but biopsies of gastrointestinal (GI) system was not indicative for a specific diagnosis such as celiac disease or inflammatory bowel disease. Eventually, he was evaluated by pediatric hematology and received intra-venous (IV) iron treatment. Resolution of anemia with IV iron treatment was suggestive for the presence of an enteropathy. He received retinoic acid treatment due to acne breakouts on his face and body 18 months ago. There was no consanguinity between his parents. His brother has hypogammaglobulinemia due to protein losing enteropathy and receives IV immunoglobulin every month. Family history revealed no similar complaints or rheumatological disease in his family.

On physical examination, swelling with pain on motion without erythema, warmth, or loss of range of motion in bilateral knee and ankle. On inspection he had ptosis and rough face with furrowing of skin on face and scalp. Besides, diffuse homogeneous, orange, folded plantar keratoderma with rough appearance of hands and clubbing on all digits were observed (Figure 1). Findings of other systemic examination were unremarkable. In the laboratory evaluation, leukocyte, lymphocyte and thrombocyte indices were within normal ranges with hemoglobin of 9.4 g/dL. Increased acute phase reactants were detected with C-reactive protein (CRP) of 94 mg/L and erythrocyte sedimentation rate of 39 mm/h. Despite normal mean corpuscular volume (83.1 fL) and serum vitamin B_{12} (215 ng/L) level, he had iron deficiency anemia with low total iron (29 µg/dL) and ferritin (12 µg/L) level. Peripheral blood smear showed no specific findings or abnormal cells. Tests for rheumatoid factor, anti-nuclear antibody, anti-extractable nuclear antigen antibodies and anti-double stranded DNA were all negative.

Acro-osteolysis and cortical thickening of the tubular bones were observed on direct radiographs. Magnetic resonance imaging (MRI) of the knees revealed bilateral increased fluid and thickened synovium with contrast enhancement in the suprapatellar bursa and joint space, and heterogeneous signal changes, edema areas and contrast enhancement were observed in the supra- and infrapatellar fat pads. In addition, diffuse signal changes were detected in the metaphysis and diaphysis of the bones forming the bilateral knee joint (Figure 2). Because of the MRI findings, bone marrow aspiration was performed for suspected malignancy and findings were unremarkable.

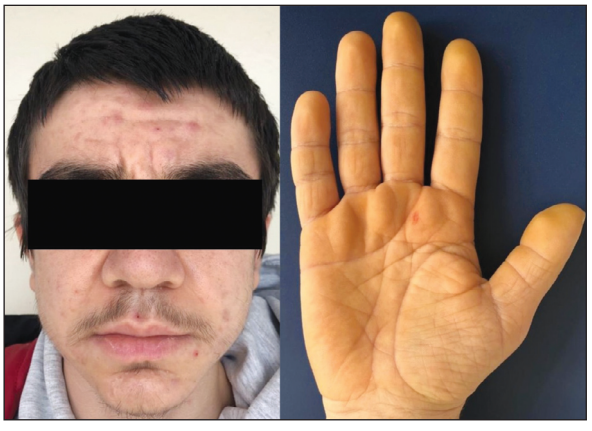

FIGURE 1: Rough face and furrowing of the skin on forehead, orange and folded plantar keratoderma.

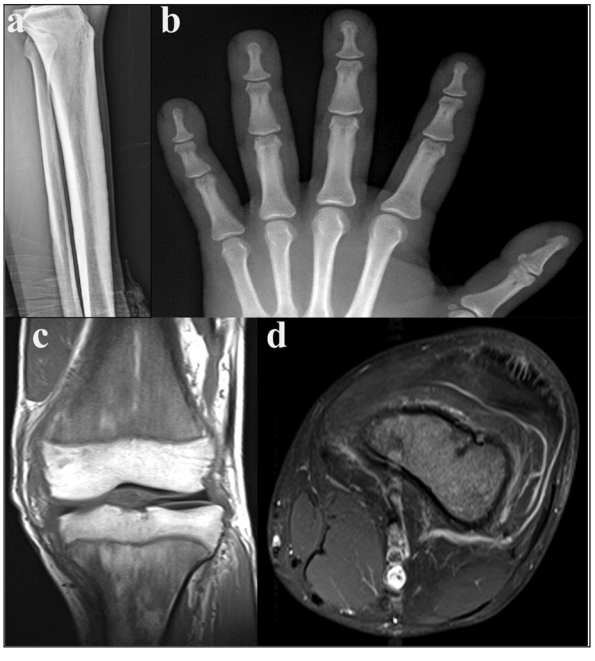

FIGURE 2: a) Radiograph reveals cortical thickening of the tibia; **b)** Direct radiography of the hand shows acro-osteolysis; **c-d)** Synovial hypertrophy, contrast enhancement and bone marrow edema in magnetic resonance imaging of the knee.

Based on clinical and radiological findings in our patient, mutation in *SLCO2A1* gene was suspected and genetic analysis was performed. Diagnosis of complete PDP with homozygous c.1660G>A (p.G554R) (p.Gly554Arg) mutation in *SLCO2A1* gene was made. Treatment with naproxen was initiated and his pain and joint swelling regressed significantly within two weeks. Also, a decrease in acute phase reactants was observed in the first month of follow up. An informed consent has been signed.

DISCUSSION

Diagnosis of PDP might be challenging especially in the presence of incomplete presentations of the disease. Torgutalp et al. presented a 20-year-old male case with PDP, in whomfirst complaints began at the age of 12 and diagnosed as juvenile idiopathic arthritis.[7] He wastreated with methotrexate and anti-tumor necrosis factor agent since then. Diagnosis was suspected with clubbing of the fingers, thickening of the bone on the direct radiographs and subperiosteal new bone formation in the MRI of the femur. Genetic analysis revealed *SLCO2A1* gene mutation, and his complaints were regressed rapidly with acemetacin, a prostaglandin inhibitor. In our case diagnosis of PDP was relatively easy due to the complete presentation of disease. But it is important to remember that presentation of the disease may be incomplete in childhood.

In a recent review of 158 patients with PDP, there was a male predominance (94%). Most common initial symptoms were clubbing (72%) and pachydermia (thickened skin) (47%). Other symptoms at initial presentation were joint pain (10.9%) and joint hypertrophy (7.2%) and GI disease (3.6%). Moreover in the course of the disease digital clubbing was developed almost all patients (98.7%). Also, disease manifestations including pachydermia, plantar hyperhidrosis, acne and cutis verticis gyrate wereseen more common than the initial presentation of the disease. Besides joint pain or hypertrophy were reported nearly half of the patients (44.9%). GI involvement over the course was not rare and reported in 17.2% of patients.[8] Our patient exhibited nearly all typical features of the disease with clubbing of the fingers, pachydermia, cutis verticis gyrate, periostosis, arthritis, acne and GI involvement.

Laboratory evaluation of these patients may reveal elevated CRP in about two third of patients, but anemia and hypoalbuminemia were relatively rare.[8]

Periostosis, commonly observed in the shaft of tubuler bones, is the imaging hallmark in PDP. Osseous resorption at the distal phalanx, known as acro-osteolysis might be present. Bone involvement tends to be symmetrical and epiphyseal involvement is more common in PDP. MRI of the bone and joint might reveal joint effusion, periosteal elevation and contrast enhancement of periosteum. Bone marrow edema could be seen rarely.[9,10] Acro-osteolysis and cortical thickening of tubular bones were observed in direct radiographies of our patient. Also MRI investigation of the knees revealed symmetrical synovial hypertrophy and joint effusion with contrast enhancement, and bone marrow edema.

Mutations of the *HPGD* gene result in impaired function of 15-hydroxy prostaglandin dehydrogenase and mutations of the *SLCO2A1* that causes defective prostaglandin transporter protein are responsible of the PDP. Both mutations lead to increased levels of prostaglandin E2.[4,11] Prostoglandins induce vascular endothelial growth factor (VEGF) secretion and changes in the bone, periosteum, skin and also digital clubbing are thought to be associated with the activity of fibroblasts, osteoblasts and osteoclasts by the influence of prostaglandins and VEGF.[12]

In a systematic review, non-steroid anti-inflammatory drugs were reported to be effective in treatment of arthritis and should be the first choice.[13] Here in, we presented this case to raise awareness of this rare genetic disease in the differential diagnosis of inflammatory arthritis. In those with HOA and arthritis, recognition of this rare genetic disease may result in better management. Just non-steroid anti-inflammatory treatment may lead to improvement of the musculoskeletal complaints, thus avoidance of more aggressive treatments might be possible. Due to multisystemic involvement of disease, multi-disciplinary approach may yield a better patient care.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hakan Kısaoğlu, Özge Baba, Mukaddes Kalyoncu;* ***Design:*** *Hakan Kısaoğlu, Özge Baba;* ***Data Collection and/or Processing:*** *Hakan Kısaoğlu, Mukaddes Kalyoncu, Özge Baba;* ***Analysis and/or Interpretation:*** *Hakan Kısaoğlu, Özge Baba;* ***Literature Review:*** *Hakan Kısaoğlu, Özge Baba;* ***Writing the Article:*** *Hakan Kısaoğlu, Özge Baba;* ***Critical Review:*** *Hakan Kısaoğlu, Özge Baba, Mukaddes Kalyoncu.*

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