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Combination csDMARD and Infliximab in Primary Hypertrophic Osteoarthropathy, a Case-Based Review

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Abstract

An 18-year-old male patient presented with excessive sweating on the palms of the hands and soles of the feet. X-ray showed periostosis in the carpal and tarsal bones. Genetic analysis revealed c.1807C>T(p.Arg603Ter), a homozygous mutation, and PHO was diagnosed. The patient was treated with dexketoprofen, methotrexate, and methylprednisolone for the first six months. No adequate response was obtained; infliximab was added to the existing treatment and continued for another six months. The number of tender and swollen joints decreased. However, a partial response was obtained. After the 12th month, dexketoprofen was discontinued, and celecoxib was added. Arthralgia, hyperhidrosis, acne and seborrhea, and minor joint arthritis responded utterly. COX inhibitors were effective on pachydermia and clubbing but did not affect arthralgia and hyperhidrosis. It seems effective in cases treated with MTX and IFX, especially on pustular lesions, arthralgia, and hyperhidrosis. We responded to almost all clinical phenotypes with combination therapy and put the patient into remission. The literature review shows that the number of patients in whom biologic therapy has been tried is very small. Our case is the first case with an almost complete response to combination therapy, and the second case was treated with infliximab.

Key words: Primer hipertrophy osteoarthropathy; pachyderma periostosis; biological treatment

Introduction

Primary Hypertrophic Osteoarthropathy (PHO), also known as pachyderma periostosis (PDP), is characterized by pachydermia, periostosis and digital clubbing (1). Clinically, approximately 20-40% of cases present with arthritis. It most commonly affects the knee, ankle, and wrist. Other principal symptoms are gradual thickening of the skin on the face and scalp (lion face), prominent forehead skin folds (cutis verticis gyrata), seborrhea and acne due to sebaceous gland hypertrophy, hyperhidrosis due to sweat gland hypertrophy and periostosis of long bones (2). X-ray is of great importance in the evaluation of PHO. Clubfinger is characterized by a process of bone remodeling that takes the form of acro-osteolysis and rarely tuftal overgrowth. Clubbing occurs primarily on the toes. Periosteal proliferation is a typical finding of the disease. PHO is characterized by joint space preservation and the absence of erosions or para-articular osteopenia (3). In 2008, Uppal et al. Genetically demonstrated that homozygous mutations in HPGD encoding 15-hydroxyprostaglandin dehydrogenase (15-HPGD) resulted in PHO (4). In 2012, Zhang et al. showed that homozygous mutations in solute carrier organic anion transporter family member 2A1 (SLCO2A1) are another pathogenic cause of PHO (5). Studies show that inheritance is both autosomal recessive and autosomal dominant (6). Both genes are involved in the prostaglandin metabolism pathway. This result suggests that high prostaglandin E2 (PGE2) levels may be involved in the pathogenesis. Prostaglandins mediate pathogenic mechanisms, particularly the inflammatory response. They are produced from arachidonate by the action of cyclooxygenase (COX) isoenzymes, and their biosynthesis is blocked by nonsteroidal anti-inflammatory drugs (NSAIDs), including those selective for COX-2 inhibition. Four primary bioactive prostaglandins are produced in vivo: PGE2, prostacyclin I2 (PGI2), PGD2, and PGF2α. EP1 (E prostanoid

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receptor 1), EP2, EP3, and EP4 subtypes of the PGE receptor. PGE2 is one of the most abundant PGs produced in the body. Studies have shown both proinflammatory and anti-inflammatory effects of PGE2 (7).

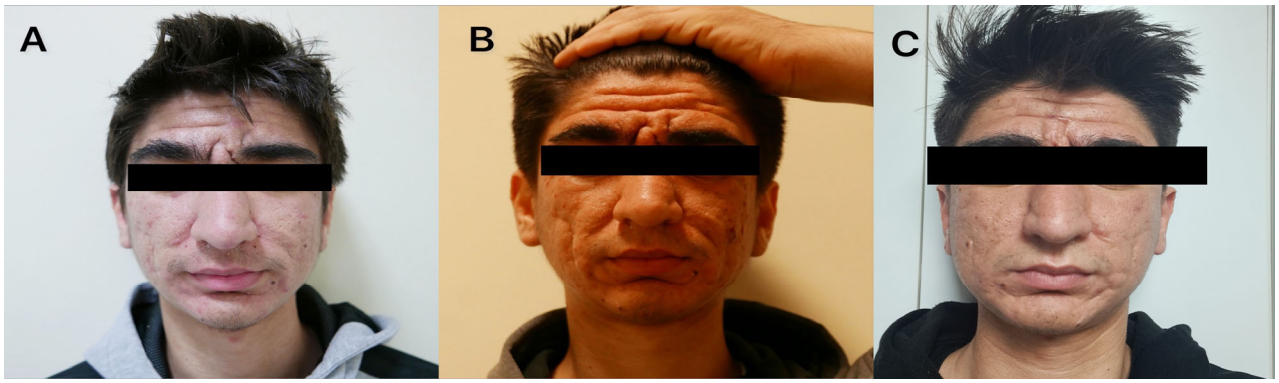

Figure 1: A) Cutis vertica gyrata at the time of diagnosis. **B)** Cutis vertica gyrata after 12 months of treatment. **C)** Cutis vertica gyrata after 18 months of treatment. Regression is seen.

Table 1: Clinical phenotypes and treatment responses of the case

Clinical phenotypes of the case and treatment responses					
Clinical phenotypes	At diagnosis	6th month	12th month	18th month	Comment
Seborea	Yes	50% decreased	Completely disappeared	Remission	Effective
Acne	Yes	50% decreased	Completely disappeared	Remission	Effective
Stick finger	Yes	Yes	Yes	Yes	Düzelme görülmedi
Arthralgia	9	4	1	0	Effective
Arthritis	20	6	6	4	Partially regressed
Joint effusion	Yes	Yes	Yes	Decreased	Partially regressed
Periostosis	Yes	Yes	Yes	Decreased	Partially regressed
Anemia	Yes	Normal	Normal	Normal	Effective
Acroosteolosis	No	No	No	No	Not evaluated
Gastric Hypertrophy	No	No	No	No	Not evaluated
Watery diarrhea	No	No	No	No	Not evaluated

Arthralgia was assessed by VAS score, Arthritis was assessed by the number of swollen joints.

EP2 and EP4 mediate the development of collagen-induced arthritis (8). The EP4 receptor also appears to play a proinflammatory role in the pathogenesis of rheumatoid arthritis (9,10). As a pro-inflammatory mediator, PGE2 regulates the cytokine expression profile of dendritic cells (DC). It plays a role in T cell differentiation. It has been shown to direct the inflammatory process toward T helper (Th)1 or Th2, depending on the type of stimulus and receptor interaction (11). A study showed that PGE2-EP4 signaling in DCs and T cells facilitates Th1 and IL-23-dependent Th17 differentiation (12). In addition, PGE2 induces a mobile DC phenotype, stimulating their migration from the lymph nodes into the circulation (13). Simultaneously, during this stimulation, PGE2 induces the expression of co-stimulatory molecules of the tumor necrosis factor (TNF) superfamily on DCs. This results in enhanced T-cell activation by TNF (14). These inflammatory mechanisms may have governed the development of the disease. In this case, we describe a rare syndrome with no established treatment. The clinical manifestation and diagnostic criteria were reviewed. Treatment approach options were staged. Based on previous studies, the effect of combined therapies on disease progression was observed. Inflammatory markers such as hemogram, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were used in diagnostic tests. Genetic testing was performed on peripheral blood samples. The patient was followed up with imaging using X-ray and magnetic resonance imaging. The patient's pain

level was obtained using Visual Analog Scores (VAS). The number of tender joints (TJC) and swollen joints (SJC) were recorded at each visit. Arthritis follow-up was evaluated using the Disease Activity Index 28 (DAS28).

Case Presentation

18-year-old male patient presented with clubbing of the fingers and toes and ankle edema. He had no history of any disease. He was not taking any medication continuously. He has had arthralgias since the age of 16. Arthralgias mainly were in the lower extremity joints. The patient had papulopustular lesions on the trunk, arms, face, and back for two years. In the last year, cutis vertica gyrate-like skin thickening had started on the face (Figure 1). The clinical phenotypes of the patient are summarized in Table 1. In addition, hyperhidrosis of the hands and soles of the feet had started in the last six months. Upon physical examination, wrists, ankles, and knees were thickened (Figure 2).

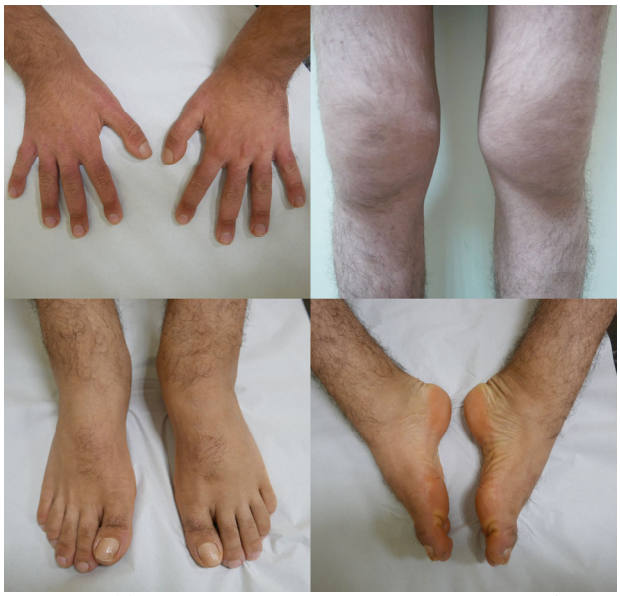

Figure 2: These are the images taken at the patient's first presentation. Clubbing of the hands and feet swelling of the knees and ankles are visible.

Rapid ultrasonographic evaluation revealed severe effusion in both knees. There were findings of tenosynovitis in both wrists and both ankles. Laboratory tests revealed anemia and elevated CRP levels. Tests sent to exclude connective tissue diseases, gonadal hormone disorders, parathyroid, and thyroid dysfunctions that caused similar clinical findings were normal (Table 2). Direct radiographs revealed cortical thickening in the middle and proximal phalanges of all fingers of both hands. Radiographs of bilateral knee joints showed diffuse cortical thickening and periosteal reactions. Bilateral foot radiographs detected Mild cortical thickening in the talus and navicular joints. The above-mentioned radiographic features

Table 2: Laboratory data

Laboratory data			
WBC	7870	IGG	22.4 (g/L)
Ly	1990	IGM	0.86 (g/L)
Hgb	10.7 (g/dL)	SAA	2.41 mg/dL
Plt	406.000	CRP	36 (mg/L)
Cre	0.67 (mg/dL)	ESR	14 (mm/h)
ANA	Negative	TSH	1.87 (mIU/L)
Anti-dsDNA	Negative	IGF-1	185 (µg/L)
Anti-Sm	Negative	GH	0.78 (ng/mL)
RF	Negative	Androstenedion	7.37 (nmol/L)
CCP	Negative	FSH	4.5 (U/L)
PTH	14 (ng/mL)	LH	9 (U/L)

WBC: White Blood Cell, **Ly:** lymphocyte, **Hgb:** Hemoglobulin, Plt: Platelet, **Cre:** Creatinin, **ANA:** Anti nuclear anticor, **RF:** Rheumatoid factor, **CCP:** cyclic citrullinated peptide, **PTH:** Parathyroid hormone, **SAA:** Serum amyloid-A, **TSH:** Thyroid stimulating hormone, **IGF-1:** Insulin-like growth factor, **FSH:** Follicle Stimulating Hormone, **LH:** Luteinizing Hormone.

were compatible with PHO. Before treatment, magnetic resonance imaging (MRI) of both ankles revealed subchondral bone marrow edema in the epiphyseal line of the tibia, fibula, talus, calcaneus, and tarsal bones. Effusion and tenosynovitis were found in the muscle-tendon sheaths around both ankles. There were also synovitis findings at the Achilles tendon attachment site. The genetic analysis sent with a prediagnosis of PHO revealed a homozygous SLCO2A1 gene c.1807C>T(p.Arg603Ter) mutation. The clinical phenotypes found in the patient are summarized in Table 2. With clinical, laboratory, radiologic, and genetic results, the patient was diagnosed with complete PHO. The patient's TJC was 20, and SJC was 16. VAS was 9, and CRP was 36 (mg/dL). DAS28CRP 6.41 was measured in the patient. Methotrexate (MTX) (15 mg/week), methylprednisolone (MP) (10 mg/day), colchicine (1 g/day), and dexketoprofen (150 mg/day) were started. Colchicine treatment was discontinued due to gastrointestinal intolerance. The patient was treated with this therapy for six months. TJC and SJC regressed to 6. VAS was 4, and CRP was 21 (mg/dL). DAS28CRP decreased to 3.62. However, there was no regression in the joint swelling in both knees, ankles, and wrists, clubbing fingers, and pachyderma. On direct radiographs, thickening progressed significantly in the metacarpal joint diaphyses.

Table 3: Literature review

Literature	Case No	Male/Female	Age	Genetics	Mutations	Treatment	Response to clinical phenotypes	Comment
Erken E et al. (6)	1	Female	23	HPGD	c.310_311delCT	NSAİD, SSz, MTX	Arthritis, Arthralgia, Joint effusion	Effective
Erken E et al. (6)	2	Male	22	HPGD	p.L104AfsX3	NSAİD, Ssz	Arthritis, Arthralgia, Joint effusion	Effective
Wójtowicz J et al. (19)	3	Male	11	No Data	No Data	NSAİD, SSz, MTX	No Clinical Response	Not Effective
Giancane G et al. (2)	4	Male	20	HPGD	c.120delA c.175_176delCT	NSAİD, SSz, MTX, ETA, ADA	Clinical response, category not clear	Effective
Giancane G et al. (2)	5	Male	21	SLCO2A1	c.754C > T + c.794C > G	NSAİD, SSz, MTX	No Response (No new joint relapse)	Not Effective
Giancane G et al. (2)	6	Female	15	HPGD	c.120delA	NSAİD, MTX	Response to joint and skin involvement	NSAID response but no MTX response
Ibba S et al. (20)	7	Male	19	No Data	No Data	MTX	No Clinical Response	Not Effective
Vaidya B et al. (15)	8	Male	28	No Data	No Data	NSAİD, MTX	Arthritis, Arthralgia, Joint effusion, skin involvement	Effective
Vaidya B et al. (15)	9	Male	26	No Data	No Data	NSAİD, MTX	Arthritis, Arthralgia, Joint effusion, skin involvement	Effective
Zhang Q et al. (21)	10	Male	18	No Data	No Data	NSAİD, SSz, MTX, TNF alpha inhibitor	No Clinical Response	Effective with zoledronic acid
da Costa, FV et al. (17)	11	Male	33	No Data	No Data	Colchicine, alendronic acid, tamoxifen, zoledronic acid, pamidronat, IFX	Clinical response, category not clear	Effective with IFX

NSAIDs–nonsteroidal anti-inflammatory drugs, Mtx–methotrexate, SSz–sulfasalazine, ETA-Etanercept, ADA-Adalimumab, IFX-Infliximab

However, arthritis and arthralgia in the metacarpal joints wholly resolved. The patient's papulopustular lesions decreased by 50%, and hemoglobulin (HGB) levels increased. Infliximab (IFX) 5 mg/kg (loading at 0-2-6 weeks followed by maintenance every six weeks) was added to the existing treatment. The patient was followed up with this treatment for six months. Tender joints disappeared utterly. However, SJC remained at 6. VAS decreased to 1 and CRP 14 (mg/dL). DAS28CRP decreased to 2.11. Hyperhidrosis regressed completely after IFX treatment. Papulopustular lesions and swelling in the small joints disappeared utterly, but swelling in the knee, ankle, and wrist joints persisted. Although there was minimal reduction in effusion in the knee joint, there was no change in the ankle joints. The patient's pachyderma findings continued to

progress (Figure 1A, 1B). On control ankle MR imaging, periostitis persisted in the distal phalanges of the foot. Diffuse thickening of the Achilles tendon was considered a sign of tendinosis and was evaluated in favor of progression. Effusion persisted in the tibiotalar joint in both ankles. Celecoxib 400 mg/day was added at this stage. After two months of combination therapy, SJC decreased to 4. VAS 1 and CRP 4 (mg/dL) decreased. DAS28CRP decreased to 1.79. Progression was also stopped with the current combination therapy. The patient's pachyderma findings regressed (Figure 1C). No complications developed.

Discussion

PHO is a rare genetic and inflammatory disorder. The pathophysiologic mechanism has yet to be fully elucidated. Therefore, there needs to be a consensus on a treatment strategy. This is the first case in the literature in which combination therapy (IFX, celecoxib, MTX) was applied. It is also the first case to achieve almost complete remission with this treatment. When we look at the pathophysiology of PHO, changes in the prostaglandin pathway have been detected due to genetic mutation. Especially PGE2 has been shown to increase in blood and urine. Vaidya B. et al. treated two cases of PHO with MTX and presented two-year results. In these two cases, they reported a response to arthralgia and regression in acute phase reactants, and they halted the progression in clubbing and pachydermia findings. However, they did not observe decreased joint effusions (15). Based on these data and pathophysiology information, we started MTX and dexketoprofen combination therapy in our patient. After six months of treatment, we could not achieve any effect except regression of pustular lesions and regression of arthralgia. However, we slowed the patient's progression and achieved a partial decrease in CRP values. It has been reported that T-lymphocytes and DC cells may be involved in the pathology through pathways triggered by PGE2 in prostaglandin metabolism. A study showed that TNF- α, IL-6, and RANKL were increased in eight patients with PHO who developed gastric hypertrophy (16). Based on this pathophysiologic mechanism, Costa et al. gave MTX and IFX combinations to patients diagnosed with PHO. In this case, the patient's VAS score decreased from 9 to 3, and inflammatory markers such as ESR and CRP decreased to the normal range. They also reported that anemia improved and joint effusions decreased. In this case, they argued that especially TNF-α may play a role in the pathophysiology of PHO (17). Based on these data, we added IFX to MTX, dexketoprofen treatment. After six months of treatment, we could only get a partial response. In our case, the findings of acne, seborrhea, hyperhidrosis, and arthralgia responded very well. However, there was the progression of periostitis and pachyderma. This result suggested that pathophysiologic mechanisms still need to be elucidated in patients with PHO. The results of a prospective study with 41 patients are interesting. Forty-one patients with PHO were treated with eterocoxib (COX-2 inhibitor) for six months, and it was proven that PGE2 levels decreased in blood serum measurements. Significant regression of pachydermia, clubbing, and joint effusions after etherocoxib has been reported. However, its effect on periostosis has yet to be proven. In addition, no effect on hyperhidrosis, pustular lesions, and arthralgia was demonstrated (18). Based on these data, we discontinued dexketoprofen and added celecoxib, another COX-2 inhibitor available in our country, to MTX and IFX treatment. With this triple therapy, we achieved almost complete remission in the patient. CRP values were measured in the normal range for the first time. We achieved regression in the patient's pachydermia findings, and DAS28CRP values decreased to the lowest value of the last 1.5 years. We achieved complete clinical remission. We searched PHO cases using medical journal databases. In particular, we searched the databases Pubmed and Web of Science. We analysed the abstracts of 72 articles. Of these, we extracted articles that reported the use of csDMARD and/or biological therapy. In total, 14 articles met the criteria. We excluded two articles because treatment outcomes were not reported. Details of a total of 11 cases are shown in Table-3. There are many case reports in the literature on the treatment of PHO. COX inhibitors, bisphosphonates, methotrexate (MTX), csDMARDs such as sulfasalazine (SSz), and biologics have all been tried. There still needs to be a precise treatment. Our review of the literature showed conflicting results. In cases 1, 1,2,3,4,5,8, and 9 in Table-3, the authors reported a partial response to MTX treatment (2,6,15,19). They mentioned it was particularly effective in arthritis, arthralgia, and effusion. Our case supported the same results. However, there are contradictory data in the literature. Especially before the diagnosis of PHO, the clinical phenotype of the disease can be confused with JIA, and rheumatologists start csDMARDs and biologics in these patients. In case number 4,

although MTX, adalimumab, and etanercept were tried with a pre-diagnosis of JIA, no response was achieved, and progression was reported (2). These data suggest that csDMARDs and biologics do not prevent disease progression. Indeed, similar results were reported in cases 6,7,10 (2,20-21). The 11th case again reported a confusing result. They reported an excellent response to infliximab for arthritis, arthralgia, and other clinical phenotypes (17). Based on this case, we added infliximab to MTX and SSz treatment and responded to most clinical phenotypes. When we added celecoxib to the current treatment, we almost put the disease into remission. We also saw regression of the skin manifestations. Our case is the second in the literature to be treated with infliximab. It is also the first case combined with csDMARD, and celecoxib was added. When we review the literature, none of the treatments tried to prevent disease development. In light of these data, each case should be evaluated individually. In addition, which of the pathophysiological mechanisms we tried to explain in the introduction is dominant in the case may be determined by genetic and epigenetic reasons. This creates severe difficulties in the choice of treatment.

Conclusion

There is no treatment option effective for all PHO clinical phenotypes. COX inhibitors seem to be effective on pachydermia and clubbing, but their effect on other manifestations has not yet been proven. They are effective in cases treated with MTX and IFX, especially pustular lesions, arthralgia, and hyperhidrosis. However, while it regressed arthritis and effusion in small joints, it did not contribute to arthritis and effusion in large joints, which we observed in our case. This result showed that different inflammatory pathways may be active in developing clinical phenotypes of patients with PHO and, therefore, the importance of clinical phenotyping. Therefore, it is essential to determine which kinetic phenotype is predominant in the patient and determine an individualized treatment strategy accordingly.

Our success with this triple therapy suggests that we can slow down the course of the disease when we control different inflammatory pathways. In the literature, single-agent or dual combination treatment strategies have been tried, which distinguishes our case from others. Can a triple combination therapy provide complete remission in this disease? This is a point that needs to be clarified. Studies with many patients are required. In addition, our knowledge about the treatments' long-term effects and side effects is limited. Multicenter studies with more patients are needed.

Declarations

Authors: BO, İHB, FY Ethical approval and consent to participate: Written informed consent was obtained from all patients.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests: The authors declare that they have no competing interests.

Availability of supporting data: All data are kept in the data center of Kahramanmaraş Sütçü İmam University Medical Faculty Hospital.

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