Clinical Case Report

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Successful treatment of pachydermoperiostosis patients with etoricoxib, aescin, and arthroscopic synovectomy

Two case reports

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Abstract

Rationale: Pachydermoperiostosis (PDP) is a rare hereditary disorder that affects the skin and bones. PDP is characterized by periostosis, digital clubbing, and pachydermia. Previous studies demonstrated that increased prostaglandin E2 (PGE2) levels resulting from defective protein degradation pathways play a crucial role in PDP pathogenesis, and males were more commonly and severely affected than females. Moreover, nearly all PDP patients suffer from refractory arthralgia. Although several different treatment modalities are used for PDP, therapy for this disease remains challenging.

Patients concerns: Two cases of PDP showing symptoms consistent with polyarthritis and arthralgia that mainly affected the knees and ankles.

Diagnoses: The diagnostic criteria for PDP include digital clubbing, periostosis, and pachydermia. The 2 patients were diagnosed as PDP based on the finger clubbing, facial cutis furrowing, knee and ankle arthritis, and radiographic evidence of periosteal proliferation.

Interventions: Patient 1 had massive joint effusion that was treated by oral administration of etoricoxib and aescin combined with arthroscopic synovectomy, whereas Patient 2 had mild joint swelling and accepted only oral medication.

Outcomes: Clinical symptoms of the 2 patients greatly improved after the treatment. During the 1-year follow-up, the patient experienced no adverse effects or recurrence.

Lessons: The therapeutic results showed that oral etoricoxib could reduce inflammation and retard progression of pachydermia, or even relieve facial skin furrowing, but had limited efficacy for arthralgia. However, oral aescin had satisfactory efficacy for arthralgia. Thus, etoricoxib combined with aescin is a safe and effective treatment for PDP. Meanwhile, arthroscopic synovectomy can be used to treat joint effusion, but had no therapeutic effect on arthralgia. Therefore, postoperative oral medications would be needed as subsequent therapy for joint problems. In conclusion, this study proposes an effective and safe treatment plan to address symptoms experienced by PDP patients.

Abbreviations: ANA = antinuclear antibody, COX = cyclooxygenase, ESR = erythrocyte sedimentation rate, hs-CRP = hypersensitive C-reactive protein, NSAIDs = nonsteroidal anti-inflammatory drugs, PDP = pachydermoperiostosis, PGE2 = prostaglandin E2, PHO = primary hypertrophic osteoarthropathy, RF = rheumatoid factor, VAS = the visual analog scale, WBC = white blood cell count.

Keywords: aescin, arthroscopic synovectomy, pachydermoperiostosis, etoricoxib

1. Introduction

Pachydermoperiostosis (PDP), also called primary hypertrophic osteoarthropathy (PHO), is a rare congenital disorder that causes periarticular tissue swelling and joint discomfort or arthralgia. Nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and colchicine are not particularly effective PDP treatments, whereas the severe arthralgia gradually resolves over several years. The diagnostic criteria for PDP include digital clubbing, periostosis, and pachydermia. Additional clinical signs and symptoms include seborrheic hyperplasia, hyperhidrosis, and arthropathy.[1,2] Symptoms usually appear around puberty, with a male-to-female ratio of 7:1, and males are more severely affected.[3] Articular manifestations of PDP appear as polyarthritis, for which a differential diagnosis of other high bone density skeletal dysplasias is sometimes required.[2]

Both autosomal dominant with incomplete penetrance and recessive inheritance of PDP occur. Increased levels of prostaglandin E2 (PGE2), which is important for eicosanoid-dependent inflammatory responses, resulting from defective protein degra-

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Figure 1. Patient 1 had facial skin thickening and furrowing, severe eyelid ptosis, and finger clubbing.

dation pathways also contribute to PDP pathogenesis.[4] Indeed, Sasaki et al[5] reported that pachydermia severity and associated histological changes correlated with serum PGE2 levels. PGE2 can promote activity of osteoblasts and osteoclasts, which are involved in acro-osteolysis and periosteal bone formation. Moreover, prolonged local vasodilatory effects of PGE2 may produce digital clubbing characteristic of PDP.

Given the central role of PGE2 in PDP pathogenesis, NSAIDs are often used to treat PDP. However, NSAIDs do not relieve arthritic symptoms.[6–8] Other treatments such as steroids and colchicine are also not particularly effective for arthralgia.[7] Arthralgia occurring in PDP may originate from active inflammation of the periosteum rather than synovitis.[9] Here we report treatment of 2 cases of symptomatic PDP with oral etoricoxib (Merck Sharp & Dohme Australia Pty Ltd, Australia) and aescin (Cesra-Arzneimittel Gmbh & Co KG, Germany) for arthritis coupled with arthroscopic synovectomy.

2. Case reports

2.1. Patient 1

A 22-year-old man with a 4-year history of painful swollen knees and ankles was referred to our hospital. He noticed marked finger clubbing and pachydermia, or facial skin thickening (Fig. 1), beginning at the age of 16. On physical examination, the patient's skin was greasy with coarse hairs. The patient also had excessive sweating and severe acne with sebaceous hyperplasia. Initial serum analyses showed above-normal hypersensitive C-reactive protein (hs-CRP) levels and an erythrocyte sedimentation rate (ESR) of 22.83 mg/L (normal range 0–3.00 mg/L) and 25 mm/h (normal range 0–15 mm/h), respectively. The white blood cell count (WBC) was 6140 mm^{-3} (normal range 3500–9500 mm^{-3}), and tests for antinuclear antibody (ANA) and rheumatoid factor (RF) were negative. Radiographic examination showed obvious endosteal and periosteal hyperostosis caused by loss of normal tubulation in the hand phalanges (Fig. 2A), as well as soft-tissue swelling and extensive, shaggy augmented periosteal ossification with cortical thickening in the tibia and fibula (Fig. 2B). The patient had no relevant family history and his parents were not clinically affected. His 30-year-old brother had similar symptoms: pachydermia with cutis verticis gyrata (Fig. 3), acromegaly, seborrheic hyperplasia, and hyperhidrosis, but he received no treatment for mild arthralgia. Based on the finger clubbing, facial cutis furrowing, knee and ankle arthritis, and radiographic evidence of periosteal proliferation, PDP was diagnosed. To treat massive joint effusion of the knees and ankles that severely limited joint mobility, the patient was given oral aescin and etoricoxib, both at 30 mg/d. After treatment for 1 month, the hs-CRP values normalized and the joint pain diminished. However, the hydrarthrosis and joint swelling remained severe, and arthroscopic synovectomy of the knees and ankles was performed. The arthroscopic findings showed villonodular

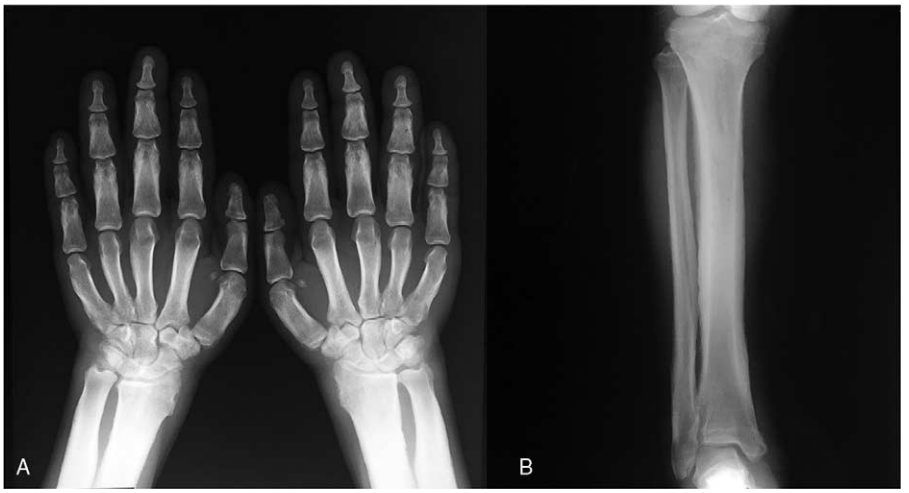

Figure 2. Radiographs of Patient 1 showed (A) loss of normal tubulation of metacarpals and phalanges; cortical thickening of metacarpals, proximal and middle phalanges; and marked soft-tissue swelling in the hands; (B) periosteal proliferation in the tibia and fibula.

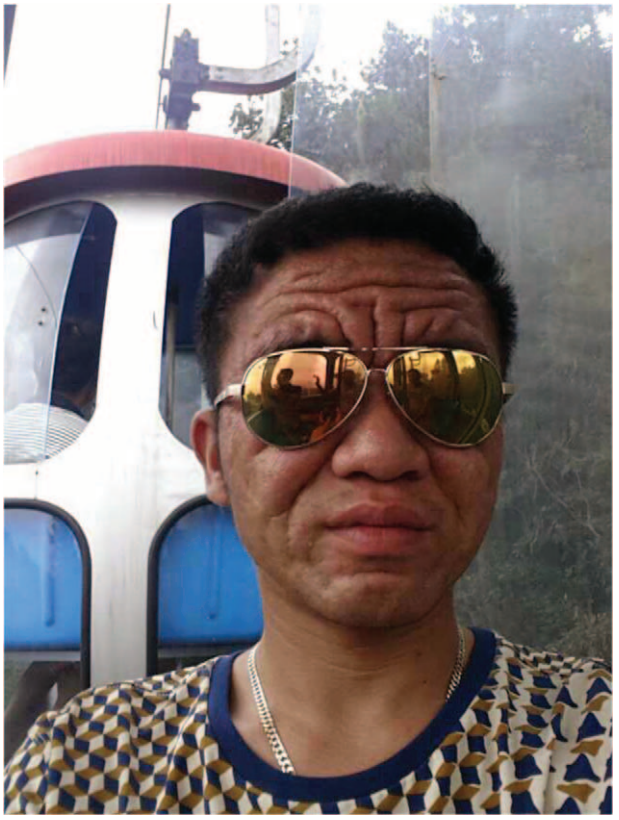

Figure 3. Patient 1's older brother showed leonine facies with thickening and deep furrowing of facial skin.

synovitis (Fig. 4). After the arthroscopic synovectomy, the knee and ankle swelling significantly decreased, but the joint pain persisted without oral medication. After treatment with 60 mg/d of etoricoxib and aescin, the hs-CRP and ESR values decreased to 2.10 mg/L and 8 mm/h, respectively. The visual analog scale (VAS) scores improved from 6 to 7 to 2 to 3, and the dosage was gradually tapered to a maintenance dose of 30 mg/d aescin and etoricoxib. During the 1-year follow-up, no adverse effects and aggravated thickening or furrowing of the facial skin was seen and the severe arthralgia did not recur.

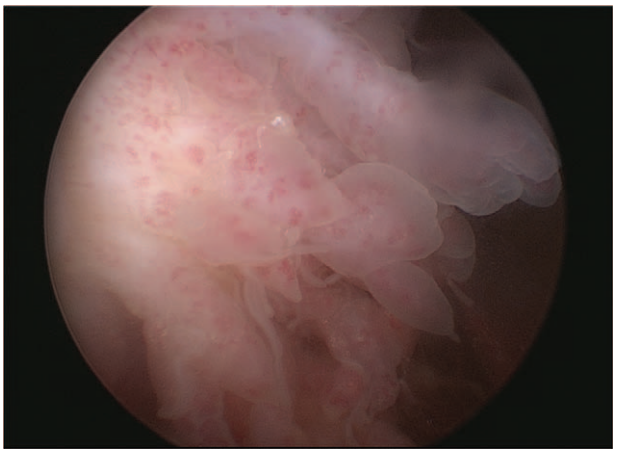

Figure 4. Arthroscopic view of affected joint synovium in Patient 1 showed marked synovial hyperplasia.

2.2. Patient 2

A 23-year-old male presented with complaints of knee joint pain since the age of 18. He noticed enlargement of both hands and feet (Fig. 5), and prominent skin folds on his forehead and cheeks beginning at age 15. He also noticed enlargement of the elbows, ankles and knees. None of his family members had similar features. Initial serum analyses showed above-normal hs-CRP levels (15.23 mg/L; normal range 0–3.00 mg/L) and normal ESR (8 mm/h; normal range 0–15 mm/h). The WBC was 6540 mm^{-3} (normal range 3500–9500 mm^{-3}), and ANA and RF tests were negative. Radiographs showed irregular periosteal hypertrophy with bone formation affecting the long bones, metacarpals, and phalanges bilaterally. Based on the major diagnostic criteria (digital clubbing, periostosis, and pachydermia),[2] the patient showed all major clinical findings and was diagnosed with PDP. Despite treatment with NSAIDs and an oral low-dose steroid, the knee and ankle arthralgia persisted. Treatment with 30 mg/d etoricoxib for 2 months lessened coarsening of facial features (Fig. 6), and the hs-CRP and ESR decreased to 1.16 mg/L and 1 mm/h, respectively. The joint swelling significantly diminished, but the arthralgia did not improve and severely affected the patient's quality of life. For pain relief, 60 mg/d oral aescin was added to the etoricoxib regimen, which resolved the joint pain 1 week later. The VAS scores improved from 6 to 7 to 1 to 2. During the 1-month follow-up, the patient halted etoricoxib for 2 weeks and oral aescin alone appeared to effectively treat joint pain. Although oral aescin dramatically relieved the joint pain, the hs-CRP level gradually increased to abnormal levels, so a maintenance dose of both aescin and etoricoxib was given to relieve arthralgia and lessen inflammation. During the 1-year follow-up, the patient experienced no adverse effects or recurrence.

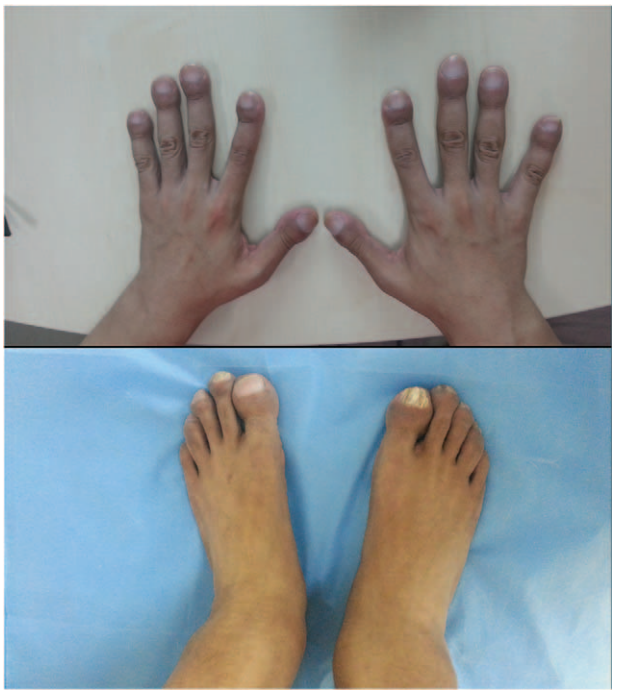

Figure 5. Patient 2 showed notable finger and toe clubbing.

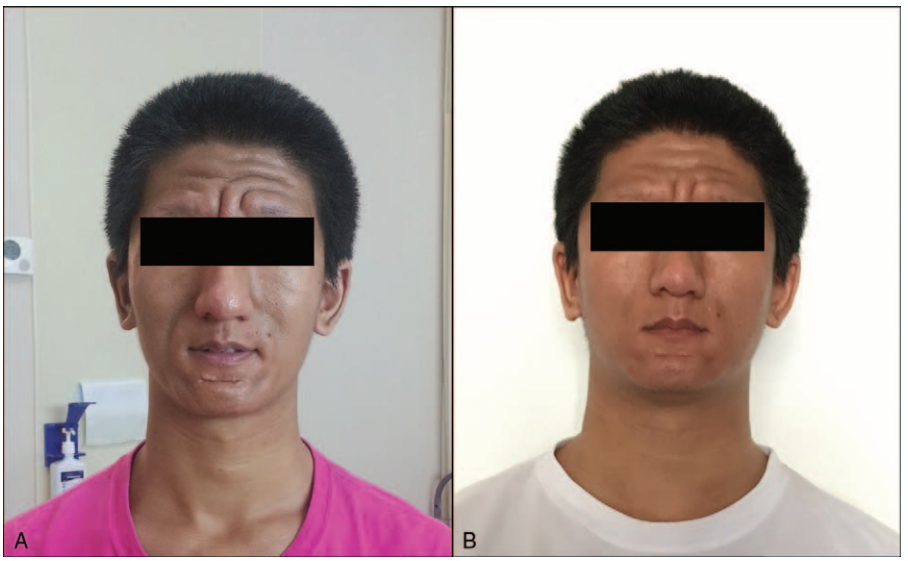

Figure 6. Facial skin furrowing of Patient 2 before (A) and after (B) etoricoxib administration for 2 mo.

2.3. Ethics approval and consent to participate

This study was approved by the Ethical Committee of the Peking Union Medical College Hospital, and informed consent was obtained from patients enrolled in this study.

3. Discussion

PDP, or PHO, is characterized by pachydermia, periostosis, and finger clubbing. This rare hereditary disease occurs predominantly in males and the onset is often at puberty. PDP diagnosis is based on typical clinical features and radiological data. The phenotypic spectrum of PDP is broad and manifests as joint involvement consisting of arthralgia, arthritis and hydrarthrosis/hemarthrosis. Nearly 40% of PDP patients also have joint effusion, but the symptoms are not particularly severe and few experience severe joint pain.[10] Other cutaneous features of PDP include seborrhea, blepharoptosis, acne, hyperhidrosis of the palms and soles, cutis verticis gyrata, eczema, erythematous lesions over the joints, polelike lower legs, and burning sensations in the hands and feet. Radiologically, acro-osteolysis, characterized by periosteal changes of the short and flat bones and ossification of ligaments and interosseous membranes, is also seen.[2]

PDP pathogenesis is associated with increased concentrations of plasma PGE2 that likely result from defective protein degradation pathways.[4] As a lipid with endocrinological activity, PGE2 can simulate osteoblast activity, promote fibroblast growth, and increase collagen and extracellular matrix production, which is consistent with bone and soft tissue findings in PDP.[11,12] Given the central role of PGE2 in PDP pathogenesis, we treated our 2 patients with etoricoxib, a cyclooxygenase (COX)-2-selective NSAID, which normalized ESR, and hs-CRP levels. Patient 2 saw lessening of the prominent forehead skin folds, but the joint pain persisted until oral aescin was added. Aescin has anti-edematous and venotonic properties, as well as significant anti-inflammatory activity that affects the cellular phase of the inflammatory process, that is, leukocyte activation.[13] Although both etoricoxib and aescin have anti-inflammatory effects, etoricoxib normalized the ESR and CRP levels, whereas aescin had superior analgesic action, likely due to its anti-edematous effect. A previous study reported that PDP-associated arthralgia can originate from active inflammation of the periosteum.[9] The nerves of the periosteum are very sensitive to tension and periosteum swelling may cause joint pain. The anti-edematous properties of aescin could relieve this tension and afford analgesia, although the actual mechanism of aescin in PDP requires further investigation.

Patient 1 had a synovectomy to treat synovitis, refractory arthralgia, and serious joint effusion. To investigate treatment of arthralgia with synovectomy, Patient 1 received no postoperative oral medications for 2 weeks. Arthroscopic synovectomy reduced joint swelling in this patient, but had no long-term therapeutic benefits. Although previous studies showed that synovectomy can reduce pachydermoperiostosis-associated arthralgia,[6,14] these studies all used synovectomy combined with medication and did not evaluate the curative effects of synovectomy alone. In this study, we observed that the knee and ankle swelling significantly decreased without postoperative medication, but no therapeutic effect on arthralgia was observed and the VAS scores did not improve, suggesting that PDP-related arthralgia is not due to synovitis.

The weaker anti-inflammatory activities of aescin relative to etoricoxib are insufficient to normalize ESR and hs-CRP levels. Thus, a combination of etoricoxib and aescin yielded more effective relief of joint pain while lessening inflammation reactions and pachydermia severity. Meanwhile, low-dose oral etoricoxib and aescin can maintain a curative effect without compromising liver and renal function, as suggested by the lack of hepatic and renal effects seen during the 1-year follow-up period.

4. Conclusions

This study evaluated etoricoxib and aescin treatment for PDP patients. Etoricoxib significantly reduced inflammation reactions and relieved or retarded pachydermia progression. Meanwhile, aescin relieved arthralgia. The results suggest that etoricoxib combined with aescin could be a safe and effective treatment for PDP. Arthroscopic synovectomy reduced joint swelling for

patients with marked joint effusion, but had no therapeutic benefit for arthralgia. Thus, in the absence of synovitis complicating marked joint effusion, we advise PDP patients not to undergo synovectomy, whereas patients with joint effusion to undergo arthroscopic synovectomy to reduce swelling and receive combined oral medications for analgesia.

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