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Case Report

CASE REPORT

Inflammatory variant of pachydermoperiostosis responding to methotrexate: a report of two cases

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Abstract

Pachydermoperiostosis is a rare genetic disorder characterized by skin thickening, digital clubbing and periostitis. The pathogenesis is incompletely understood and there are no proven treatments for its manifestations. Although arthritis has been reported in 20–40% cases, most are non-inflammatory in nature and usually treated symptomatically with steroids or NSAIDs. We report two cases of pachydermoperiostosis with inflammatory variant of arthritis and raised inflammatory markers who were treated with tapering dose of prednisolone for 6 weeks and maintained on long-term low dose methotrexate like rheumatoid arthritis and followed for 2 years. In both cases, methotrexate was well tolerated and helped in maintaining symptomatic improvement and slowed the disease progression with significant steroid and NSAID sparing effect. We concluded that there exists an inflammatory subtype of disease where methotrexate can be beneficial.

INTRODUCTION

Pachydermoperiostosis (PDP) or primary hypertrophic osteoarthropathy is a rare genetic disorder characterized by pachydermia, periostitis and digital clubbing [1] with 7:1 male predominance [2]. Most patients have autosomal dominant inheritance with variable penetration [3] but genetic mutation of HPGD gene has been seen in recessive cases [4]. Pathogenesis of PDP is incompletely understood and theories postulate increase collagen synthesis from active proliferating fibroblast leading to increased levels of various growth factors [5]. No definite therapeutic option has been proven to be effective in the management of this disorder. Arthritis has been reported to occur in 20–40% of cases of PDP [6], however inflammatory markers and synovial fluid studies are usually suggestive of non-inflammatory arthritis. We report two cases of PDP in young males presenting with inflammatory joint pain and effusion, positive inflammatory markers and satisfactory response to disease modifying anti-rheumatic drugs.

CASE 1

A 28-year-old male patient presented with pain and swelling of small joints of hands, wrists, bilateral knees, digital clubbing and coarsening of facial features (Figs 1 and 2). Onset was insidious at age of 14 years with gradual increase in the size of fingers, swelling of knees and eyelids. Since last 18 months, swelling, pain and stiffness of his metacarpophalngeal joints and knees got worse in the morning. Physical examination revealed pachydermia with thickening and furrowing of his forehead folds and cheeks (cutis verticis gyrata), bilateral blepharoptosis, bilateral hand active synovitis with knee effusion, digital clubbing and palmoplantar hyperhidrosis. Synovitis and effusion in knee joint were confirmed by ultrasonology of knee joint with power Doppler application (Fig. 3). X-rays revealed periosteal bone formation which confirmed the diagnosis of hypertrophic osteoarthropathy (Fig. 4). Routine laboratory and immunological markers were unremarkable except for raised ESR (62 mm in first hour; normal range: 0–10 mm/hour) and CRP (80 mg/l; normal range: 0–6 mg/l) levels (Table 1). We used

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Figure 1: Case1 showing thickening of forehead and cheek skin.

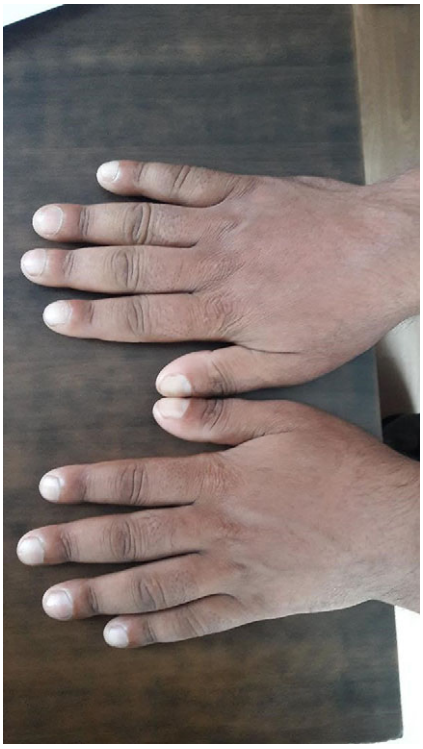

Figure 2: Digital clubbing and finger enlargement.

DAS28 scores used in rheumatoid arthritis to measure his disease activity. His baseline DAS 28 score was 5.87 (high activity) which decreased to 2.45 (remission) after 2 years of treatment. Other core-set variables are shown in Table 2. He was started

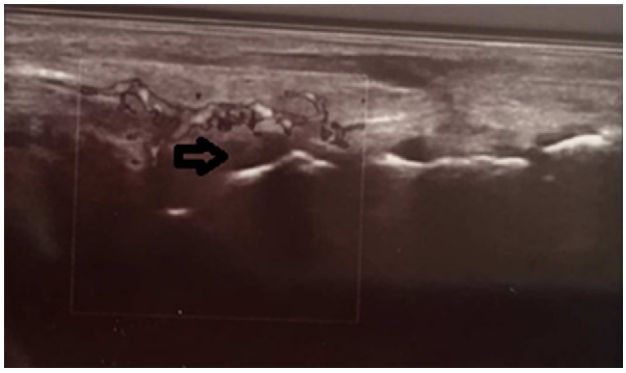

Figure 3: USG of knee joint of case 1 showing marked synovial hypertrophy (arrow) with positive Doppler activity and effusion.

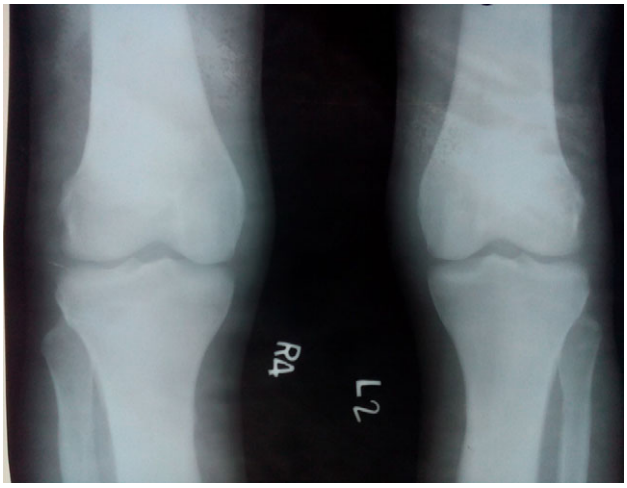

Figure 4: X-ray showing periosteal bone growth.

on prednisolone starting from 20 mg per day and tapered off over 6weeks in combination with methotrexate 15 mg and folic acid 5 mg per week and was followed till 2 years. He tolerated methotrexate well. He had intermittent flares with need of short course steroids twice in 2 years. His DAS28-CRP has remained low (2.45) and his clubbing and joint enlargement did not show any further progression; skin thickening has slightly regressed on his forehead and has not progressed in other areas (Figs 5 and 6).

CASE 2

A 26-year-old male patient presented to us 2 years ago with prominent skin folds on his forehead and cheeks beginning at the age of 18 years accompanied by pain, swelling and enlargement of multiple joints and finger tips, periorbital swelling and hyperhidrosis. Swelling was first noted in the ankles which gradually progressed to involve bilateral wrist and metacarpophalyngeal joints. Family history of chronic arthritis in father was given but without a definite diagnosis. He also has controlled hypothyroidism on 100 mcg thyroxine. He was taking oral hydroxychloroquine 200 mg daily and on/off NSAIDs since last 15months. Recently, he had worsening of pain and swelling of the joints with marked restriction of movement of bilateral

Table 1: Baseline lab invesitigation reports of cases 1 and 2

Invesitigations	Case 1	Case 2	Normal range
WBC	4200	6140	3500–9500 mm^{-3}
LFT			
SGPT	40	26	(<50 U/l)
SGOT	28	34	(<50 U/l)
Total bilirubin	0.8	0.6	~1.2
Direct bilirubin	0.4	0.4	~0.2
ALP	280	350	50–300 U/l
KFT			
Blood urea	40	32	10–50 mg/dl
Serum creatinine	1.0	0.8	0.5–1.4 mg/dl
Serum uric acid	6.2	5.6	3.4–7.0 mg/dl
Sodium	138	144	135–155 mmol/l
Potassium	3.8	4.1	3.5–5.5 mmol/l
Total protein	6.4	7.9	6–8.5 gm/dl
FBS	100	92	100–125 mg/dl
TSH	2.5	1.3	0.5–5.0 mU/l
fT3	3.5	4.9	3.1–6.0 pmol/l
fT4	13.6	19.4	11.0–21.0 pmol/l
Prolactin	108	110	425 mIU/l
LH	–	2.9	2–5.3I U/l
FSH	–	5.3	1.8–5.1 IU/l
Testosterone	22	19.7	9–29 nmol/l
fasting GH	2.4	0.45	0–3 µg/l
ANA	Negative	Negative	
Anti-CCP	Negative	Negative	
RF	Negative	Negative	
CRP	80	65	0–6 mg/l
ESR	62	55	0–10 mm/h

Table 2: Follow-up data of case 1

	Baseline	3 months	6 months	2 year
CRP mg/l	80	10	5.8	5
ESR mm/h	62	30	32	28
Tender joint count	8	0	1	0
Swollen joint count	5	2	2	1
DAS28-CRP	5.87	2.78	3.45	2.45

Figure 5: Follow-up photos of same patient after 2 years.

ankle and wrist joints. Physical examination revealed greasy skins with coarse hairs, cutis verticis gyrata of scalp and forehead, bilateral mechanical ptosis and hyperhidrosis(Figs 7 and 8) with joint hyperlaxity, bilateral swollen ankle and wrist joints with mid-carpel tenderness. Radiographs showed irregular

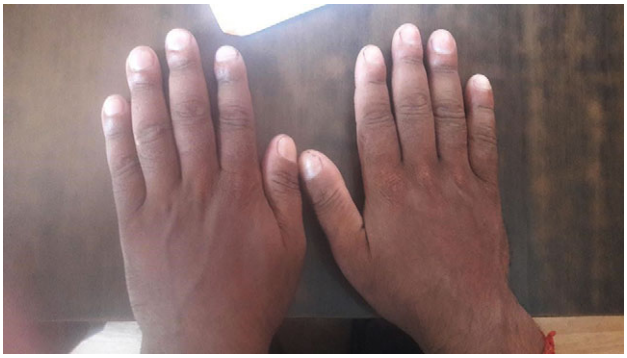

Figure 6: Follow-up of same patient after 2 years (hands) showing same findings with slightly.

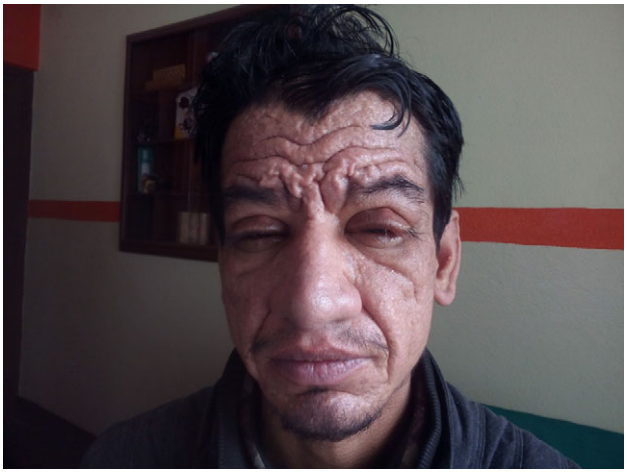

Figure 7: Case 2 (cutis verticis gyrate, blepharoptosis and facial furrowing).

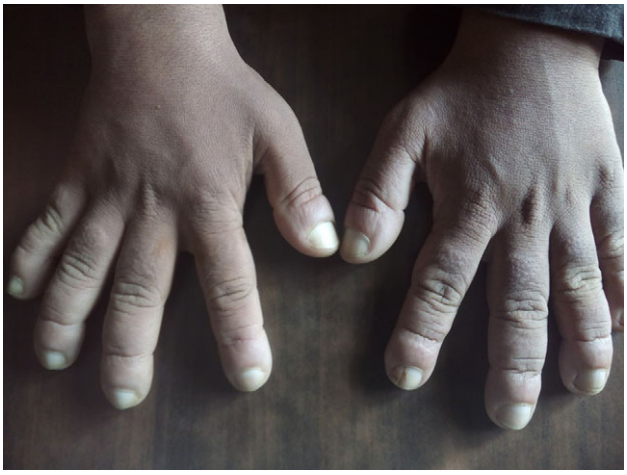

Figure 8: Hand enlargement of second case (pachydermia, clubbing, enlargement).

periosteal hypertrophy with bone formation affecting the long bones, metacarpals and phalanges bilaterally (Figs 9 and 10). Ultrasonology of wrist joint with power Doppler application showed synovial hypertrophy with positive Doppler signals (Fig. 11). Laboratory examinations revealed elevated ESR (55 in first hour; normal range: 0–10 mm in first hour) and CRP (65 mg/l;

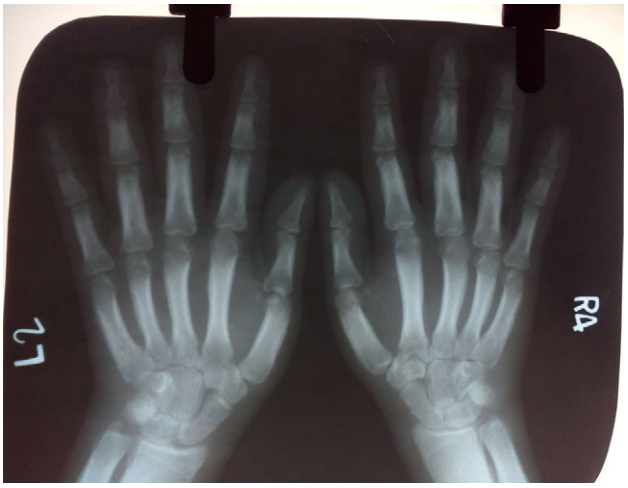

Figure 9: X-ray hands of second case (cortical thickening with periosteal bone formation in proximal phalange).

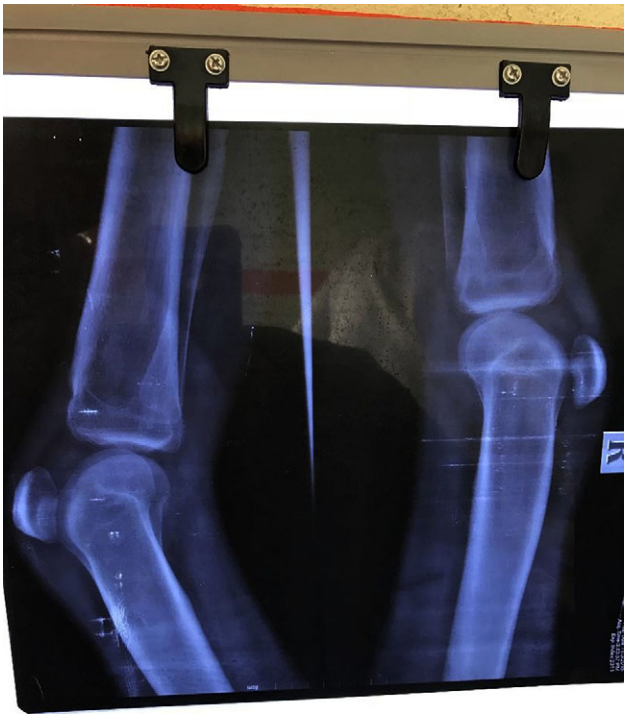

Figure 10: X-ray of long bones of case 2 (cortical thickening with tibial periosteal bone formation).

normal range: 0–6 mg/l) as shown in Table 1. Based on the major diagnostic criteria (digital clubbing, periostosis and pachydermia), he was diagnosed as PDP with inflammatory arthritis with high disease activity (DAS 28 score 5.65). He was started on oral prednisolone starting from 20 mg per day, gradually tapered off over 6weeks in combination with methotrexate 15 mg and folic acid 5 mg per week. Though he responded well at 3 months (DAS 28 score: 2.71), at 6 months of treatment he flared again with DAS 28 score 4.38 and his methotrexate was increased to 20 mg/week with a bridging course of steroid. During next 1 year follow-up, no severe flares or adverse effects of methotrexate was observed though he kept having minor arthralgias of knees. At the end of second year, he had low disease activity with DAS

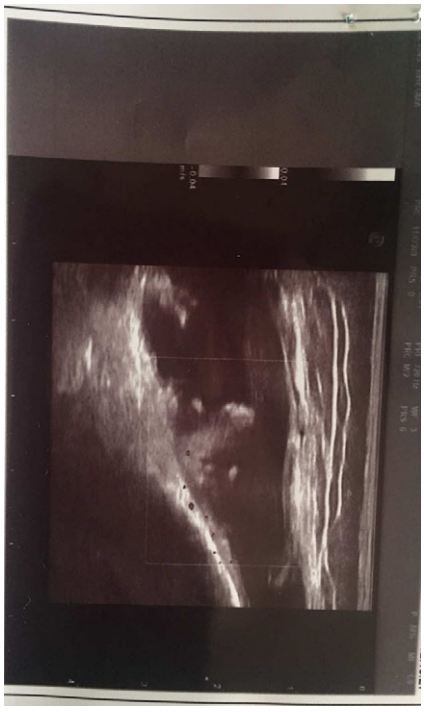

Figure 11: Ultrasonology of wrist joint of case 2 showing synovial hypertrophy (arrow) with marked Doppler activity.

Table 3: Follow-up data of case 2

	Baseline	3 months	6 months	2 years
CRP mg/l	65	8	12	4.8
ESR mm/h	55	28	22	26
Tender joint count	6	0	4	0
Swollen joint count	6	2	2	2
DAS28-CRP	5.65	2.71	4.38	2.55

28 score of 2.55. His baseline and follow-up disease activity indices are shown in Table 3. Further progression of thickening or furrowing of the facial skin was also not seen.

DISCUSSION

PDP, also known as primary hypertrophic osteoarthritis or Touraine-Solente—Gole syndrome, is a rare genetic disorder with mainly autosomal dominant inheritance. The disorder mainly affects males with onset at childhood or early teens and has a progressive course till 5–20 years. Various genetic mutations have been described in patients affected with PDP. Though various pathogenic mechanisms and responsive cytokines and growth factors have been reported, none are confirmatory [7]. This uncertainty in pathogenic pathway and rarity of disease leads to a gray-zone in the therapeutic options. Various reports have described the use of bisphosphonates [8], raloxifene, NSAIDs and cochicine to alleviate the rheumatic symptoms associated with the disease [9]. Few authors have even tried methotrexate and biological treatment with limited or no success [10]. Synovectomy has also been described in patients who failed biological treatment [8]. In addition, other than cosmetic surgery, no effective treatment has been reported in literature for skin changes.

We hypothesize that there is a subgroup of PDP patients who present with classical inflammatory findings along and raised inflammatory markers; the presentation in both our patients was rheumatoid-like but could not be classified as seronegative rheumatoid arthritis as they did not fulfill the ACR/EULAR 2010 criteria. These patients are likely to respond to methotrexate and other disease modifying drugs in terms of rheumatic symptoms. Also, we found slight subjective change in skin thickening in both our patients. We used DAS28 scores to objectively monitor the disease activity in these cases. It was seen that not only the overall score but also the core-set variables showed significant and sustained improvement with DMARDs. The knee joint effusions were particularly refractory to treatment. Moreover, the side-effect profile and dose responsiveness to methotrexate were not very different from what we generally see in rheumatoid patients. It is possible that suppression of active inflammation, inhibition of fibroblast growth and thus reduction in cytokine and growth factors induced by methotrexate are responsible for this effect. Our observation in two cases was not powered enough to comment on improvement in skin changes.

CONCLUSION

Inflammatory subsets of PDP patients might respond to long-term low dose methotrexate therapy and thus may have significant steroid and NSAIDs sparing effect.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

FUNDING

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ETHICAL APPROVAL

Ethical approval was given by Ethical Review Committee of National Center for Rheumatic Disease via letter number CR-01/18.

CONSENT

Informed written consent was taken from both patients to publish their case reports and photographs without disclosing their identity.

GUARANTOR

Dr Binit Vaidya is nominated as the guarantor for the report.

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