

Arthroscopic Synovectomy in a Patient with Primary Hypertrophic Osteoarthropathy

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= 국문초록 =

내시경적 활막제거술을 시행하여 활막염 증상이 호전된 일차성 비후성 골관절증 1예

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일차성 비후성 골관절증(Primary hypertrophic osteoarthropathy) 혹은 경피골막증(pachydermo-periostosis)은 곤봉형 수지, 골막주변 비후 그리고 피부와 두피가 두꺼워지는 연조직의 변화를 특징으로 하며 남자에게서 좀더 흔한 매우 드문 질환이다. 이차성 비후성 골관절증(secondary hypertrophic osteoarthropathy)은 원발성에 비해 비교적 흔하며 악성종양, 선천성 심질환 또는 소화기 질환과 같은 다양한 기저질환과 동반되어 나타나는 것이 특징이다. 저자들은 곤봉형 수지, 깊은 주름이 잡힌 이마, 다한증과 활막염의 특징적인 임상증상을 보인 26세 남자에서 일차성 비후성 골관절증을 진단하였으며 우측 슬관절의 지속적인 활막염과 관절종창으로 인해 내시경적 활막제거술을 시행하여 증상이 호전되었으므로 이를 문헌고찰과 함께 보고하는 바이다.

Key Words: Primary hypertrophic osteoarthropathy, Synovectomy

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INTRODUCTION

Pachydermoperiostosis (PDP) is a rare disorder of hereditary nature characterized by coexistence of pachydermia, digital clubbing and periosteal proliferation of the tubular bones. PDP is often used synonymously with primary hypertrophic osteoarthropathy (pHOA) in contemporary medical literature. In its more common form known as secondary HOA (sHOA), underlying disorders of pulmonary, cardiac, gastrointestinal origin or other systemic diseases are usually evident. Although

pHOA is a self-limited condition, recurrent arthritis can be debilitating and often poses challenge to clinicians. Information on the optimal treatment of pHOA is currently very limited and based on several anecdotal reports only. We report a case of pachydermoperiostosis with typical clinical, pathologic and radiographic features. In addition, arthroscopic synovectomy resulted in a favorable clinical outcome.

CASE REPORT

A 26 year-old-man was referred to our rheumatology



Fig. 1. (A, B) Clubbing of fingers and toes. (C) Plain radiograph shows soft tissue swelling of the fingers. (D) Soft tissue edema and effusion of knees (right > left), and enlarged ankles. (E) Deep furrowing of forehead.

clinic via orthopedic service for peculiar physical appearance and abnormal radiographs. The patient initially presented 2 months ago to the orthopedic clinic seeking medical attention for the right knee pain after minor trauma, which was found to be due to patella fracture. The patient exhibited marked clubbing of fingers and toes (Fig. 1A, B), and the radiograph of the hands showed soft tissue swelling (Fig. 1C). Accentuated furrowing and skin thickening of the forehead were also noted (Fig. 1E). Synovitis with effusions was present in both knees with a greater degree on the right and both ankles were enlarged (Fig. 1D).

The patient stated that his hands and feet grew disproportionately since puberty. Patient reported excessive sweating in the hands and feet for the past 3 years. No other family members are reportedly affected. This physical disfigurement has never given rise to any pain

or discomfort in the past. Remarkably, the patient dutifully completed 26 months of mandatory military service 4 years ago which demanded high level of physical activity.

Our physical examination confirmed the initial findings. The rest of the physical examination was non-remarkable. Radiographic examination depicted diffuse periosteal reaction in the bilateral femurs, tibias, and fibulas with a moderate amount of bilateral knee effusions (Fig. 2A, C). Bone scintigraphy revealed increased periosteal uptake in the bilateral tibias, radii and ulnas, indicative of active periosteal bone formation, and focal active bone lesion in the right patella indicated healing stage of patella fracture (Fig. 2B). MRI of the right knee revealed a large effusion and irregular thickening of synovium (Fig. 2D). Hypertrophic osteoarthropathy was diagnosed on the basis of clinical



Fig. 2. (A) Plain radiograph of lower extremity demonstrates irregular shaggy diaphyseal cortical thickening (arrows). (B) Bone scan shows increased periosteal uptake in the bilateral tibias, radii, and ulnas. Focal active bone lesion in the right patella consistent with previous fracture. (C) Knee radiograph shows periosteal and cortical thickening of tibia and fibula. (D) MRI of the right knee reveals a large effusion and irregular thickening of synovium.

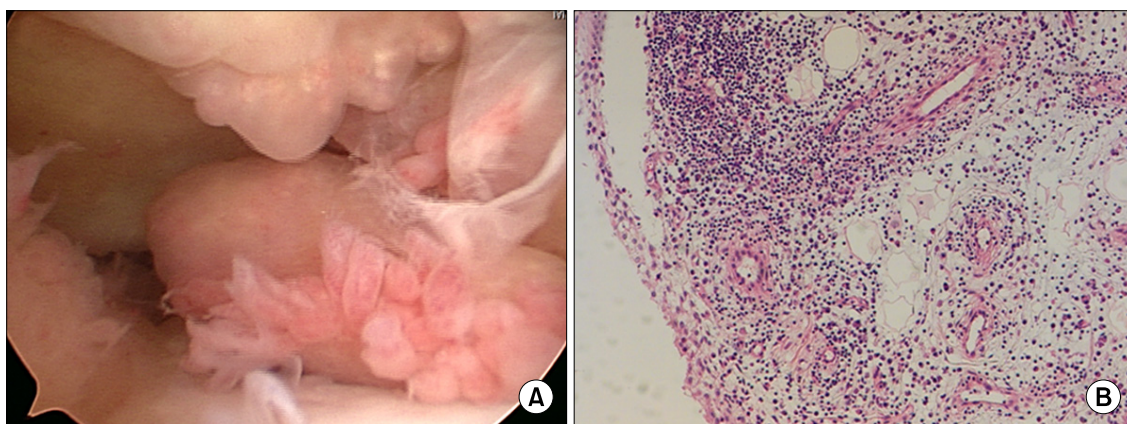


Fig. 3. (A) Knee arthroscopy shows proliferative villonodular synovitis. (B) Chronic perivascular inflammatory infiltrates is observed in the synovial tissue ($\times 100$, H&E stain).

and radiographic features. Comprehensive diagnostic workup in search of secondary causes was launched.

On laboratory examination, CBC exhibited mild anemia with hemoglobin of 12.2 g/dL, metabolic panel including liver enzymes were within normal range. Erythrocyte sedimentation rate was 37 mm/hr (normal range 0~22 mm/hr), CRP 4.34 mg/dL (normal range 0~0.3 mg/dL), negative rheumatoid factor and positive HLA-B27 antigen were noted. Synovial fluid analysis showed non-inflammatory pattern with WBC count of $180/\mu\text{L}$, 22% lymphocyte and 0% polys. Gram stain and AFB stain were negative, bacterial and fungal cultures did not grow any organisms. 2-D echocardiography, liver ultrasonography and computed tomography of chest and abdomen did not disclose any underlying lesions. Esophagoduodenoscopy revealed inactive chronic gastritis. *H. pylori* was not identified. Colonoscopy was not performed due to lack of diarrhea, hematochezia and abdominal pain. Sella turcica appeared normal on the skull radiograph. Sacroiliac joints did not show any sign of inflammation on plain radiograph and bone scintigraphy. Growth hormone was suppressed to 0.19 ng/mL (expected normal range 0.5~2.3 ng/mL) after glucose challenge. Insulin-like-growth factor was normal at 144.3 ng/mL. TSH and free T4 level were also normal.

On the basis of clinical features including digital

clubbing, deep furrowing of facial skin, arthritis of the knees and ankles, periosteal bone formation on radiographs, along with the absence of any discernable secondary causes, primary hypertrophic osteoarthropathy was finally diagnosed. Recurrent large synovial fluid accumulation with persistent synovitis of the right knee despite ongoing non-steroidal anti-inflammatory drug (NSAID) therapy persuaded us to perform arthroscopic synovectomy. Low leukocyte count in the synovial fluid did not justify intra-articular steroid injection. Arthroscopic finding revealed proliferative villonodular synovium (Fig. 3A) and histology findings showed hyperplastic synovium with chronic active inflammation (Fig. 3B).

Arthroscopic synovectomy combined with non-steroidal anti-inflammatory therapy resulted in clinical improvement with resolution of synovitis. Novel treatment modalities including bisphosphonate and tamoxifen therapy were fully considered but held due to the absence of any symptoms of arthritis.

DISCUSSION

HOA was first reported in 1868 by a German physician Nikolaus Friedreich, when he described the cases of 2 brothers affected with 'hyperostosis of the entire skeleton' (1). However, French physicians

Touraine, Solente, and Golé are largely accredited for their accurate description of HOA without any causative underlying disorders (2). Thus, it is known in continental Europe as the Touraine-Solente-Golé syndrome but is commonly referred to as pachydermoperiostosis or pHOA. Reported cases of sHOA are not uncommon, yet pHOA is still rarely encountered. The precise incidence and prevalence of pHOA are still unknown.

pHOA is reported to be inherited in an autosomal dominant pattern with incomplete penetrance, but this observation remains controversial. Analysis of published pHOA families suggests genetic heterogeneity with a coexistence of two inheritance patterns (autosomal dominant and autosomal recessive). Divergent clinical features and disease severity can be of assistance in differentiating between these inheritance patterns (3). Major histocompatibility (MHC) antigens appear to be unrelated to the disease susceptibility. Studies of human leukocyte antigen (HLA) typing in cystic fibrosis patients revealed no association with HOA development in these subgroup of patients (4). Our case was considered to exhibit a sporadic pattern based on the absence of any family history. A positive HLA-B27 in our patient appears to have no clinical significance based on the absence of inflammatory back pain and sacroiliitis in bone scintigraphy or pelvis radiograph.

The main clinical features of pHOA are somewhat variable and include digital clubbing, palmoplantar hyperhidrosis, periostitis, thickening of the scalp and facial skin with deep furrows and accentuated nasolabial folds. Male is predominantly affected with more severe clinical manifestations. It typically appears during childhood or adolescence, often around the time of puberty, and progresses slowly for about ten years. Natural history of pHOA is often self-limited and has an active adolescent phase followed by a quiescent adult phase (5).

At the extreme end of the clinical spectrum, massive thickening and furrowing of the skin of the forehead and scalp resembles the gyral pattern of the brain, a

condition known as cutis verticis gyrata. The upper eyelids are also thickened. Typical facial features may resemble that of acromegaly and tends to emerge only after adolescence. Joint involvement characterized by periarticular swelling, asymmetric arthritis and effusions are commonly encountered. Joint effusions are relatively non-inflammatory (6). Other clinical features include, but are not limited to, seborrhea, periungal erythema and oily skin.

Diagnosis of pHOA is purely one of exclusion. Major underlying lesions that may predispose patients for secondary HOA are listed in Table 1. pHOA is usually, but not always, distinguishable from secondary form by the extent of skin involvement. Coarsening of the scalp and face tends to be more pronounced in the primary form. On the other hand, in the secondary HOA, disease onset is delayed with mean age of 60 years, arthralgia tends to be more pronounced in contrast to our patient, and the rate of disease progression is slower. In majority of cases, sHOA is reversible with removal of primary causative lesion.

Radiographic features, however, are essentially identical. Radiological studies have indicated that, for primary and secondary hypertrophic osteoarthropathy alike, the degree of periosteal reaction depends on the

Table 1. Major underlying diseases of secondary hypertrophic osteoarthropathy

Pulmonary	Bronchogenic carcinoma
	Mesothelioma
	Bronchiectasis
	Lung abscess
	Interstitial lung disease
	Cystic fibrosis
Cardiac	Congenital cyanotic type heart disease
	Subacute bacterial endocarditis
	Myxoma
Gastrointestinal	Inflammatory bowel diseases
	Intestinal tuberculosis
	Polyposis of colon
	Amebic and bacterial dysentery
Hepatic	Biliary cirrhosis
	Hepatopulmonary syndrome

duration of the disease rather than its cause (7). Periostosis is limited to the diaphysis in the initial phase with relatively fewer bones involved. With longer disease duration, widespread periostosis involves the metaphysis and epiphysis. Longer disease duration is suggested by the thicker and more extensive periosteal reaction on the radiograph (7). Bone scintigraphy is a useful diagnostic modality in the active phase of the disease but is of limited value during remission (6). The role of magnetic resonance imaging (MRI) in the detection and determination of chronicity of periostitis has been also emphasized during the past several years.

Differential diagnosis of pHOA includes thyrotoxicosis that may cause thyroid acropachy, acromegaly, paget's disease and syphilitic periostitis. Careful attention to the physical appearance, clinical course and radiographic features makes the diagnosis of pHOA unmistakable.

Pathophysiology of HOA remains largely obscure. Several theories have been proposed including autonomic dysfunction with sympathetic bias (8) and dysfunctional fibroblast proliferation (9). Increased circulating levels of vascular endothelial growth factor (VEGF) in patients with HOA may lead to localized vascular proliferation associated with platelet/endothelial cell activation (10). Bianchi et al. (11) found high levels of nuclear steroid receptors, increased cytosolic estrogen receptors in patients with pHOA. They suggested from this observation that the increased tissue sensitivity to circulating sex-steroids could induce enhanced tissue EGF/transforming growth factor alpha production and utilization, resulting in hypertrophy of affected tissues. Interestingly, estrogen receptor antagonist, tamoxifen citrate, has been used and resulted in alleviating arthritic symptoms as well as improvement in hyperhidrosis (12). Nevertheless, the exact pathophysiologic mechanism needs to be further elucidated.

Unfortunately, effective treatment modality for pHOA is currently unknown due to the lack of controlled data, and is based largely on the anecdotal reports. Conven-

tional treatment regimen includes NSAIDs, colchicine or intra-articular steroid injection to the affected joints. Non-inflammatory joint involvement makes the use of systemic steroids difficult to justify. Novel treatment approaches include bisphosphonate therapy which has been reported to be of benefit in alleviating arthritic symptoms (13,14). The mechanism of action is suggested to operate through anti-inflammatory effect of bisphosphonate, as previously demonstrated by aminobisphosphonate incadronate in adjuvant-induced arthritis (15). As aforementioned, tamoxifen citrate therapy may prove to be an effective treatment modality in the future.

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