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Journal

Dermatology Online Journal, 21(6)

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Publication Date

2015

DOI

10.5070/D3216027827

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Letter

Pachydermoperiostosis and bladder cancer

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Dermatology Online Journal 21 (6): 18

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Abstract

Pachydermoperiostosis or the Touraine-Soulente-Golé syndrome is a rare monogenetic disorder characterized by pachydermia, periostosis and digital clubbing accounts for approximately 3~5% of all patients with hypertrophic osteoarthropathy. Missense mutations in *SLCO2A1* and *HPGD* genes could plausibly underlie the pathogenesis of pachydermoperiostosis. Patients have usually a favorable outcome with very few cases associated with cancer. Herein, we report the first case of a patient with pachydermoperiostosis associated with bladder cancer.

Letter to the editor

A 38-year-old male had progressive enlargement of his hands and fingers since late childhood, which stabilized by the time he was 30 year-old. History was unremarkable apart from heavy drinking, he took no regular medications, and none of his parents and sons reported similar symptoms. Examination showed broadened fingers and toes with soft-tissue hypertrophy and ballon configuration of the distal ends (Figure 1). X-ray and magnetic resonance imaging of the hands confirmed the findings (Figure 2). Skin creases were mildly thickened and deepened over his glabella. Hand and feet motion was normal as was the rest of physical examination. We ruled out all causes of secondary HO upon history, clinical examination and findings of laboratory and imaging studies. At a follow-up visit one year later, clinical examination was unchanged however the patient complained of several episodes of hematuria. Work-up revealed an undifferentiated urothelial cancer of the bladder which was surgically excised.

The association of hypertrophic osteoarthropathy (HO) with pachydermia, i.e. skin thickening and grooving particularly over the face and scalp, is referred to as pachydermoperiostosis (PD) or the Touraine-Soulente-Golé syndrome [1,2]. This is a rare monogenetic disease that starts during adolescence and accounts for approximately 3~5% of all HO cases [3]. Patients may have all PD features but cases with predominant pachydermia and no or minimal features of HO or predominant HO and negligible pachydermia are reported [1,2]. When HO is the predominant or lone feature of the syndrome it is important to rule out other differentials. An average of several years elapses from onset to diagnosis and severe phenotypes of pachydermia with leonine facies and cutis verticis gyrata, i.e. cerebriform convolutions of the scalp resembling brain surface, are seen almost exclusively in men [1,2]. Skeletal changes are generally symmetrical, with the axial skeleton being usually spared. Swelling and pain over large joints could be aggravated by alcohol intake [4]. Ligament calcification, joint effusion, and joint and muscle contractures are late events in the disease course [1,2].

Mechanistic pathways of PD are poorly understood. The excessive bone remodeling, collagen deposition and osteoid matrix formation are driven by unchecked fibroblast and macrophage activation [3]. Bone resorption and acro-osteolysis combined with new subperiosteal bone formation are the ultimate cause of the widened ends of distal digits. Missense mutations in *SLCO2A1*

and HPGD genes could plausibly underlie PD pathogenesis through modulating inflammation, prostaglandins, and bone and collagen metabolism [5-10]. Endothelium activation and synovium hyperplasia are triggered by the up-regulated CD200/CD200R1 pathway [11].



Figure 1. Soft-tissue hypertrophy and ballon configuration with terminal broadening of the fingers of both hands.



Figure 2. Frontal radiograph of the hands demonstrating a bilateral bulbous configuration of the ends of fingers with soft-tissue clubbing. Neither acro-osteolysis nor periosteal new bone formation are visible. On the left fifth distal interphalangeal joint there are small periarticular calcifications (Panel A). Soft tissue thickening, joint narrowing and osteophytosis are well demonstrated by magnetic resonance imaging (Panel B).

Treatment of pachydermoperiostosis is not established but colchicine, steroids, biphosphonates, isotretinoin, and tumor necrosis factor-blockers can be considered depending on the patient's condition; their use however is not validated [1,2]. Advanced cases could improve with plastic surgery, synoviectomy and correction of bony deformities. Long-term outcome is unknown, however

clinical decompensation is uncommon. Very few cases of PD patients in whom a cancer developed during follow-up have been described however it could be a major cause of morbidity and mortality [12-14]. Our report is the first case of pachydermoperiostosis associated with bladder cancer. Whether patients with pachydermoperiostosis are exposed to a greater risk of cancer is unclear and underlying mechanisms remain to be fully elucidated. Activation of platelets and endothelial cells and the release of growth factors such as vascular endothelial growth factor could be an important pathway of cancer growth in PD patients.

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