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Incomplete form of pachydermoperiostosis: A case report.

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Abstract :
Pachydermoperiostosis (PDP), also known as primary hypertrophic osteoarthropathy (PHOA), is a rare condition often inherited and characterized by a multifaceted mode of genetic transmission. Its precise aetiology remains unclear. The classic manifestation includes thickened skin (pachydermia), skeletal changes (periostosis), and clubbing of the digits (acropachia). We present a case study of a 30-year-old male with a decade-long history of polyarthralgia primarily affecting the hands, feet, and to a moderate extent, both knee joints. Despite multiple consultations, he was initially misdiagnosed with unspecified joint pain. This case aims to delineate the clinical features, diagnostic criteria, and underscore the necessity of a comprehensive diagnostic approach, given that pulmonary neoplasms, either primary or metastatic, are the leading cause of secondary HOA. Additionally, bone scintigraphy emerges as a sensitive modality for detecting skeletal involvement. This paper aims to enhance medical staff awareness of this disorder to facilitate prompt diagnosis and appropriate management, given its infrequent occurrence and consequent tendency towards misdiagnosis.

Key words: pachydermoperiostosis, primary hypertrophic osteoarthropathy, digital clubbing,

1. Introduction :

PDP is a rare genetic disease with a debated mode of transmission and unclear pathogenesis. It is characterized by both osseous and cutaneous manifestations. It was first described in 1868 by Friedreich, and later in 1935, Touraine, Solente, and Gole identified pachydermoperiostosis as the primary form of hypertrophic osteoarthropathy, distinct from secondary hypertrophic osteoarthropathy, often of neoplastic origin [1]. The hereditary nature of the primary form is acknowledged, despite the fact that only about 25% to 38% of cases can actually be linked to a family history of the disease. Secondary HOA accounts for approximately 95% of cases, with PHOA comprising the remaining 5% [2]. Here we present an incomplete form case of primary hypertrophic osteoarthropathy, with the intention of

familiarizing medical practitioners with this condition and ensuring prompt diagnosis and treatment.

2. Case Report:

We present a 30-year-old man who presented with polyarthralgia primarily affecting hands, feet, and to a moderate extent the knees, evolving over a period of approximately ten years, during which he consulted several colleagues without a precise diagnosis. On examination, there was hypertrophied fingers and toes extremities with drumstick appearance consistent with digital clubbing (Figure 1).

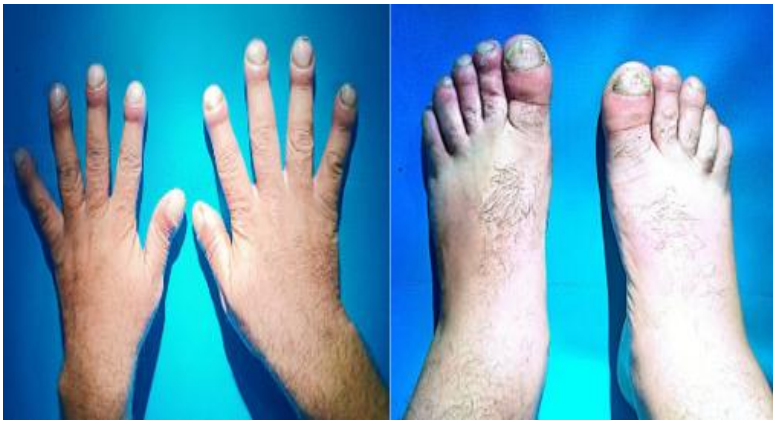

Figure 1: Both hands and feet bulbous enlargement of fingers and toes

Metacarpophalangeal, interphalangeal, and metatarsophalangeal joints were tender with positive squeeze test bilaterally, but non swollen. Cardio-pulmonary examination was unremarkable. Laboratory investigations showed negative acute phase reactants. The complete blood count, kidney and liver function tests, phosphocalcic balance were within normal limits. Rheumatoid factors and antinuclear antibodies were negative. Muscle enzymes were normal; serologies for hepatitis A, B, C, HIV and brucella were negative. Thyroid and adrenal function tests were normal, and protein electrophoresis was normal. Acromegaly was ruled out with a growth hormone level of 0.05 ng/ml (normal range: 0.97 to 4.70 ng/ml). Plain X-rays of the hands, feet, and knees revealed metaphyseal-diaphyseal periosteal apposition in long bones with increased corticomedullary index and soft tissue hypertrophy (Figure 2).

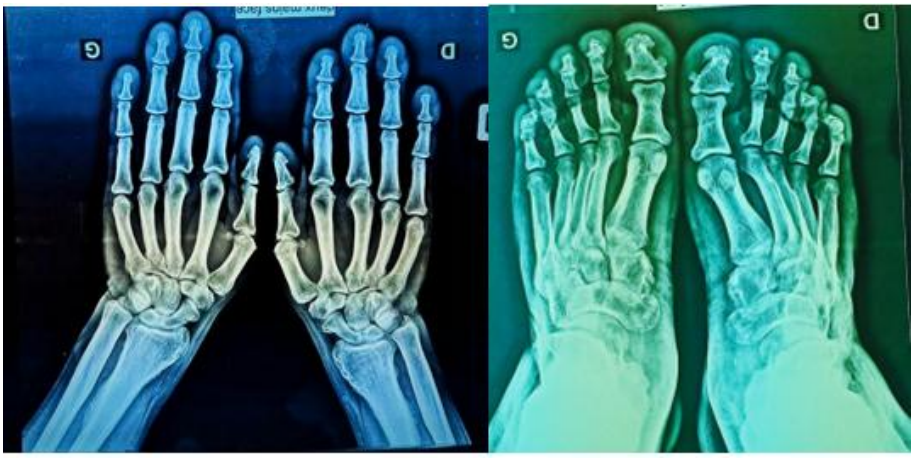

Figure 2 : Plain X-rays of the hands, feet, and knees revealed metaphyseal-diaphyseal periosteal apposition in long bones with increased corticomedullary index and soft tissue hypertrophy.

Computed tomography (CT) scan of the abdomen and pelvis was unremarkable. Bone scintigraphy revealed diffuse increased uptake throughout the skeleton, particularly pronounced in the distal extremities of the upper limbs, including the hands, forearms, and shoulders, as well as in the spine and knees (Figure 3).

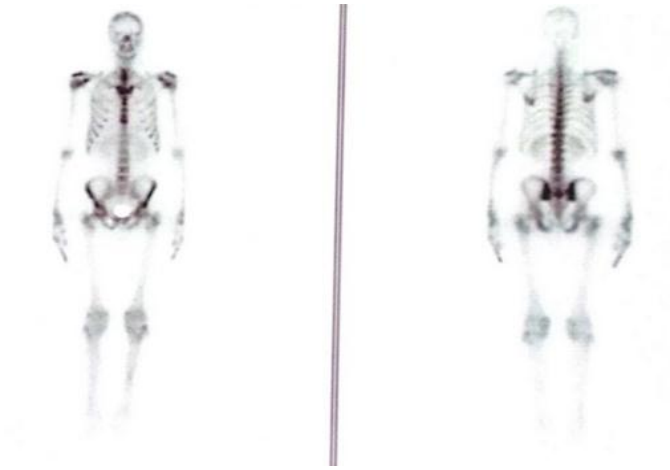

Figure 3: Bone scintigraphy revealed diffuse increased uptake throughout the skeleton, particularly pronounced in the distal extremities of the upper limbs, including the hands, forearms, and shoulders, as well as in the spine and knees.

A diagnosis of primary pachydermoperiostosis was made based on two criteria: digital clubbing and clinical and radiological evidence of periostosis. There was no family history of similar cases. The patient was treated symptomatically with nonsteroidal anti-inflammatory drugs (NSAIDs), resulting in relative improvement of symptoms.

3. Discussion :

POAH, a rare genetic disorder, has been reported in 78 cases in the literature up to 1980 [2]. It is characterized by the association of periostosis and predominantly distal pachyderma, such as cutis verticis gyrata and/or clubbing, predominantly affecting males [3]. Typically, the disorder manifests during childhood or adolescence and progressively worsens before stabilizing [4]. The primary form of OAH accounts for 3 to 5% of all cases of hypertrophic osteoarthropathy [5]. Interestingly, there appears to be a clear male predominance, as evidenced by a report by Jajic et al in 2001 which included only 5 female cases out of 76 patients with PDP [6].

Despite our incomplete understanding of the mechanism underlying the pathogenesis of POAH, recent genetic studies have revealed mutations in genes encoding the transport and catabolism of prostaglandins (PG), particularly PGE2. This suggests that impaired PGE2 metabolism plays a crucial role in the development of OAH [7]. However, the specific responsible gene(s) have yet to be identified. It has been observed that patients carrying these mutations exhibit higher levels of PGE2 in their serum and/or urine, further confirming their involvement in the pathophysiology of POAH [8, 9].

POAH mode of inheritance is autosomal recessive [10]. The genotype/phenotype correlation indicates that patients with SLCO2A1 mutations tend to develop symptoms at a later stage, but with greater severity, and are more likely to present cutis verticis gyrata and joint manifestations compared to those with HPGD mutations [11,12]. It is worth noting that no racial predilection has been found, as observations of the disorder have been reported on all continents.

The age of onset of the disease typically falls between 10 and 25 years, with our observation being a case at 21 years of age. Clinically, the disease is characterized by osteoarticular manifestations, such as arthralgia, and thickening and hypertrophy of the extremities, along with clubbing of the fingers and toes. In some incomplete forms, as observed in our case, the cutaneous signs may be absent, and the disease primarily presents with clubbing accompanied by osteoarticular manifestations.

According to its clinical features, PDP can be classified into three forms :

1- Complete (digital clubbing, pachydermia, and periostosis),
2- Incomplete (no pachydermia), and
3- Fruste form (prominent pachydermia with few skeletal manifestations) [13].

Clubbing, characterized by a bulbous deformity of the fingertips, often considered as the primary presenting manifestation in the majority of OAH cases (figure) [14]. This condition results from oedema and soft tissue hypertrophy, leading to a drumstick-like appearance due to rocking of the nail bed. Although clubbing is typically symmetrical, it can also occur unilaterally or affect only a few digits. Importantly, clubbing is usually not associated with pain in the vast majority of cases.

The arthralgias are not systematically present. They are often of moderate intensity, evolving in flare-ups. Joint effusions can also be observed, affecting medium and large joints. Arthrocentesis shows a fluid of variable composition, often pauci-cellular, termed "mechanical." However, there is neither hypertrophy of the synovial membrane nor exudation of inflammatory cells in the synovial fluid. This reflects the fact that OAH is neither an inflammatory joint disease nor a proliferative synovial disease [15].

Periostosis is the primary radiological sign of the condition. It manifests as periarticular pain, usually bilateral and symmetrical, predominating at the extremities of the limbs. The bones most frequently affected are the tibiae, fibulae, radius, and ulnae. The phalanges of the hands and the metatarsals are less commonly affected [9]. The overall examination is normal, particularly the cardio-pulmonary examination, and osteoarticular complaints are the main reason patients seek medical consultation; they are found in 68.5% of cases [6].

Plain x-rays of the hands, feet, and knees show periosteal reaction, bilateral, symmetrical metaphyseal-diaphyseal periosteal apposition of long bones with an increase in the corticomedullary index and soft tissue hypertrophy, which, according to Laredo et al., particularly affects the diaphysis, but extends to the metaphysis and epiphyses of long bones [16].

- **Bone scintigraphy** allows mapping of bone involvement throughout the skeleton. Although some authors have described a correlation between disease duration, morphology, and extent of periostosis on radiographs, a similar relationship with bone scintigraphy has not been found.
- **Positron emission tomography (PET)** can also show symmetric hypermetabolic activity along the cortex of tubular long bones, especially in the lower extremities. In some cases, a significant accumulation of 18F tracer in a particular tumor or internal organ may indicate a possible secondary origin of HOA.

According to Borochowitz et al criteria [17], the diagnosis of PDP is established with at least 2 out of the 4 following criteria:

- Family history
- Pachydermia,
- Digital clubbing,
- Clinical or radiological manifestations of periostosis.

Normal laboratory findings are a major argument in Favor of the diagnosis. Our patient met two criteria (digital clubbing and clinical and radiological manifestations of periostosis), and therefore was diagnosed as an incomplete form of PDP.

- ***Differential Diagnoses:***

Several pathologies present with multifocal periosteal reaction that may mimic the radiological appearance of PHOA. Various characteristics help clinicians and radiologists refine the diagnosis, including the type and anatomical distribution of periosteal reaction, as well as the presence or absence of bone destruction and soft tissue changes.

Thyroid acropathy and acromegaly are among the differential diagnoses of HOA. Thyroid acropathy typically occurs after the treatment of Graves' disease, particularly following thyroidectomy or thyroid resection. Patients may also exhibit digital clubbing, pretibial myxoedema, and exophthalmos. Periosteal reaction in thyroid acropathy primarily affects the bones of the hands and feet. Unlike HOA, the tibia, fibula, radius, and ulna are generally not involved [18].

Distinguishing this syndrome from acromegaly could be done on the basis of clinical characteristics and laboratory results. Unlike PDP, acromegaly manifests with noticeable enlargement of facial, cranial, and limb bones, as well as jaw protrusion, accompanied by increased levels of insulin-like growth factor-1 and a positive outcome in the oral glucose tolerance test [19]. Paget’s disease, psoriatic arthritis and rheumatoid arthritis as well should be considered in differential diagnosis [20]. Other differential diagnoses include voriconazole-induced periostitis, hypervitaminosis A, or neoplastic pathologies such as leukaemia or lymphoma [21]. Various processes, both benign and malignant, have been documented in association with PDP. These encompass conditions such as facial epidermoid carcinoma, hypertrophic gastritis, peptic ulcer, gastric adenocarcinoma, Crohn's disease, and myelofibrosis. Due to soft tissue and bones hypertrophy (mass effect), complications may manifest, including ptosis, nerve compression, hearing impairments, kyphosis, arthrosis, femoral head osteonecrosis, and carpal tunnel syndrome [22].

Prognosis: Although often considered as a benign disorder, with almost normal Life expectancy, many patients develop multiple functional or aesthetic complications.

Treatment is primarily symptomatic, involving the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics. In cases of recurrent effusions, intra-articular corticosteroid injections are commonly used. Surgical synovectomy or synoviorthesis may be considered in refractory cases or frequent relapses. Japanese authors have reported a case of a 24-year-old patient with pachydermoperiostosis treated for arthralgia with tamoxifen citrate (20 mg per day), resulting in pain regression within a few days and excellent outcomes at a 5-month follow-up, without significant side effects [16]. Bisphosphonates, as osteoclast inhibitors, appear to be a highly promising therapeutic avenue [23].

4. Conclusion :

PHOA is a rare genetic disorder. It is crucial to distinguish it from its secondary form, particularly associated with cardiopulmonary diseases and malignancies, such as lung carcinoma. Advances in genetic diagnostics of genes implicated in primary HOA have led to a better understanding of its pathogenesis. Further genetic studies are necessary to better elucidate this condition and provide therapeutic solutions, which currently remain purely symptomatic, primarily relying on analgesics and NSAIDs. Given its infrequent occurrence and consequent tendency towards misdiagnosis, medical practitioners need to be cognisant of these rare diseases.

Conflict of interest: The authors have declared no conflicts of interest related to this article.

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