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Case Report

Orthopaedic manifestations of Proteus syndrome in a child with literature update☆

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ABSTRACT

Background: Proteus syndrome is a rare developmental disorder of unknown aetiology. It is a disorder characterized by postnatal overgrowth affecting multiple tissues. Proteus syndrome is most frequently manifested in skeletal changes. As manifestations of Proteus syndrome are highly variable, and many are found in other overgrowth syndromes, and due to inconsistent application of diagnostic criteria, the literature has more reports of patients misdiagnosed than correctly diagnosed. The purpose of this study is to report the clinical and radiographic patterns of affection of the musculoskeletal system in Proteus syndrome in the light of the proposed diagnostic criteria and cases reported in the literature.
Methods: The clinical and radiographic musculoskeletal characteristics of a child with Proteus syndrome are illustrated along with a literature update. The orthopaedic manifestations in our patient are correlated to cases and proposed diagnostic criteria reported in the literature.
Results: The study of the presented case and review of available literature show that there tends to be a highly characteristic pattern of skeletal abnormalities in Proteus syndrome.
Conclusion: The rarity of Proteus syndrome and the variability of signs make the diagnosis challenging. Clinical and radiographic examinations are important contributors to the diagnosis. The clinical utility of the reported cases is significantly dependent on consistent application of diagnostic criteria that augment diagnostic accuracy. The present case reinforces the need for supplementary musculoskeletal imaging modalities to be implemented in the diagnosis of Proteus syndrome.

1. Introduction

The clinical, radiological, and biochemical characterizations of rare skeletal diseases facilitate the discovery of pathways and processes involved in skeletal patterning, growth, and homeostasis (Tosi and Warman, 2015). Proteus syndrome (PS) causes asymmetric, disproportionate, and severe postnatal overgrowth, particularly bone, in a mosaic pattern. Although skeletal features predominate, the disease may affect any tissue derived from any of the three germinal layers (Biesecker, 2006). PS is a rare condition with an estimated prevalence of one in 1 million people worldwide. PS is caused by a somatic activating mutation in AKT1 (Lindhurst et al., 2011). Rate of overgrowth and resultant distortion of skeletal structures can be overwhelming. A key attribute of the overgrowth is that it tends to alter significantly the architecture of the affected bones, commonly affecting periarticular regions. The disorder causes severe morbidity and early mortality (Slavotinek et al., 2000). The rarity of the syndrome, the wide spectrum of presentation, the lack of an easily available diagnostic test, and the occurrence of syndromes with similar phenotypes contribute to the diagnostic challenge. The diagnosis of PS is kept based on clinical features, and radiological findings (Biesecker, 2006). Unfortunately, the literature has more reports of patients misdiagnosed than correctly diagnosed (Biesecker, 2006). Given the present difficulty in diagnosing PS, this study describes the clinical and radiographic musculoskeletal characteristics of a child with PS. The orthopaedic manifestations of our patient are correlated to cases and proposed diagnostic criteria reported in the literature.

2. Case report

A five year old boy presented to our outpatient clinic. The parents noticed that a rapid, progressive overgrowth of their child began at 24 months of age, followed by significant body distortion. The boy was born full term and had a birth weight of 4.5 kg. The boy was

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second in birth order of a non-consanguineous marriage. The perinatal history was unremarkable. There was no family history of similar conditions. No history suggestive of delayed mental or motor milestones of development was encountered. No history suggestive of seizures or hearing difficulty was reported.

2.1. Non-orthopaedic manifestations

The patient's standing height measured 146 cm; greater than the 97th percentile for height. The sitting height measured 89.5 cm. The patient exhibited macrocephaly. The facial profile demonstrated a long face and dolichocephalic skull. Webbing of the neck was noticed. Almost all cutaneous manifestations were observed over the left side of the body. Cerebriform connective tissue nevi were detected over the left hand. Patchy hyperpigmentation was detected over the left side of the neck, left scapular region, left upper limb and left groin.

2.2. Orthopaedic manifestations

The overgrowth was bilateral and asymmetrical, involving all four limbs and spine. A mild dorsal scoliotic deformity was detected (Fig. 1A, B, C). The left side of the body was overgrown in contrast to the right side. Lower limb length discrepancy of 7 cm was found. The left lower limb was overgrown 5.5 cm from the femur and 1.5 cm from the tibia (Fig. 2). Mild upper limb length discrepancy was also noticed.

There was free, painless, active and passive joint range of motion of all four limbs. Focal musculoskeletal distortion in the form of patellar bony overgrowth of the left knee joint and macrodactyly of the left index finger and thumb were noticed (Figs. 3, 4A, B). The left knee showed mild valgus deformity. Macrodactyly of the left index was associated with joint stiffness. Otherwise, no other deformities were detected. Neurological examination revealed unremarkable findings. Firm nodular painless swellings were found in relation to the left side of the neck and planter surface of left foot toes.

A skeletal survey of the axial and appendicular skeleton was performed to characterize and evaluate the extent of the disease. In general, the patient's enlarged bones had a normal shape and contour (Fig. 5A, B). Examination of the cervical and dorsolumbar spine revealed dysmorphic and asymmetric vertebral bodies (Fig. 6A, B). Our patient was informed that data concerning the case would be submitted for publication. The authors declare that no conflict of interest exists. No financing was received for this study. The local ethical committee authorized the conduct of this study.

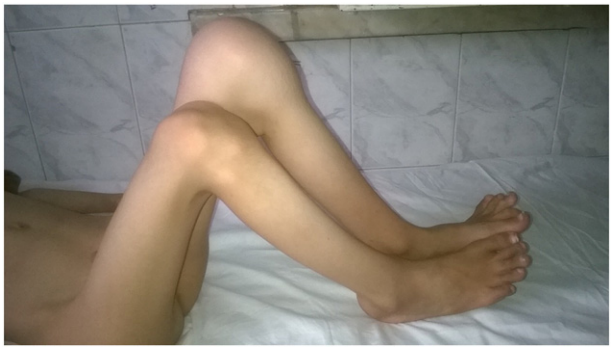

Fig. 2. Limb length discrepancy was mostly femoral.

3. Discussion

The rarity of the PS, the wide spectrum of presentations, the lack of an easily available diagnostic test and the occurrence of overgrowth syndromes with several overlapping clinical manifestations can represent a diagnostic and therapeutic challenge (Neylon et al., 2012). Several classifications have been developed in an attempt to facilitate the diagnosis of these syndromes; however, these attempts have been hindered by the syndrome's several overlapping clinical manifestations (Visser et al., 2009). Neylon et al. proposed a classification of overgrowth syndromes by ordering them according to their typical timing of clinical presentation as follows: (a) syndromes exhibiting overgrowth in the neonatal period and (b) overgrowth syndromes usually identified in childhood, as PS (Neylon et al., 2012). Our patient exhibited overgrowth during childhood. Thus, he met the diagnostic criteria of PS. Popescu et al. (2014) presented a patient that satisfied the diagnostic criteria of PS but exhibited lower limb-length discrepancy of 3 cm at birth. We assume that this finding may be interpreted as a reflection of disease severity rather than a misdiagnosis of PS. Although patients with PS characteristically exhibit overgrowth manifestations in childhood, it seems that this finding is not universal.

Biesecker proposed PS revised diagnostic criteria, based on clinical features and radiological findings. The general attributes delineate the non-specific features of PS by requiring that all patients have a mosaic

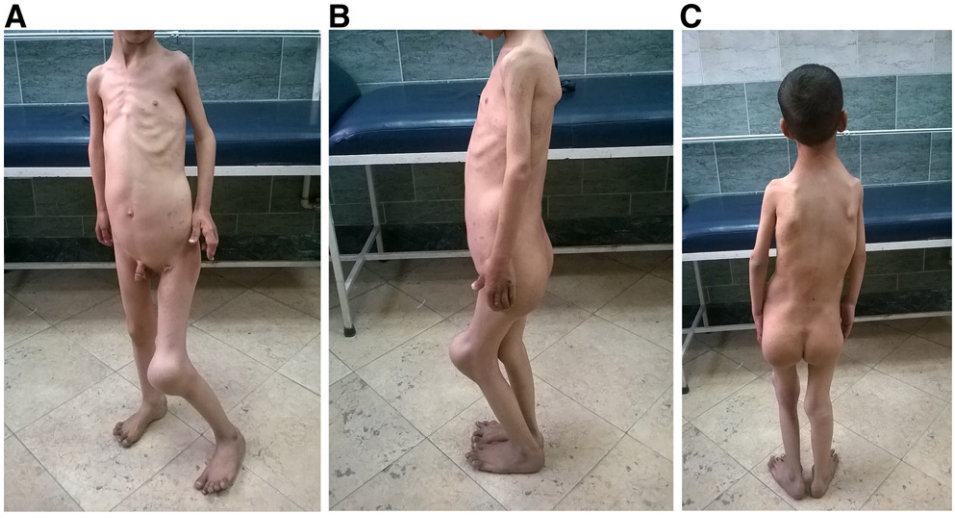

Fig. 1. (A, B, C): A five year old boy with Proteus syndrome. Note the generalized overgrowth, upper and lower limb length discrepancy, localized limb distortion of the left knee (A), postural flexion deformity of the left knee (B), and mild dorsal scoliotic deformity (C).