Bone Reports 3 (2015) 104–108

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Case Report

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

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ARTICLE INFO

Article history:
Received 12 June 2015
Received in revised form 9 September 2015
Accepted 23 September 2015
Available online 26 September 2015

Keywords:
Overgrowth syndromes
Rare bone disease
Musculoskeletal

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

☆ The authors of the current study declare that no conflict of interest exists. No financing was received for research on which our study is based.
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http://dx.doi.org/10.1016/j.bonr.2015.09.004

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.

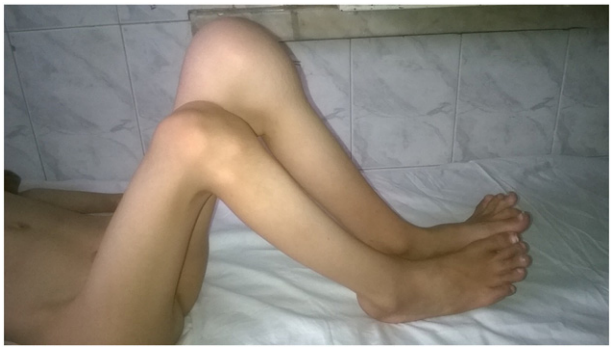

Fig. 2. Limb length discrepancy was mostly femoral.

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

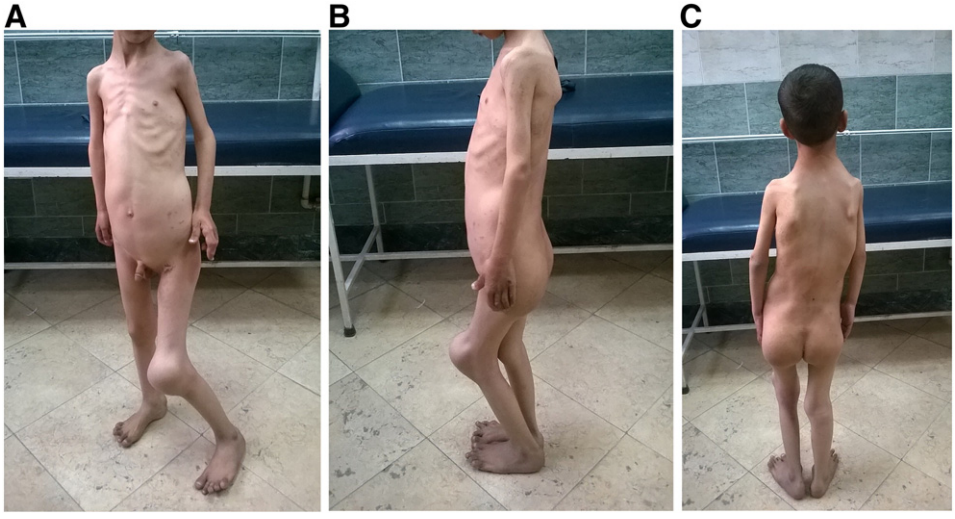

Fig. 1. (A, B, C): A five year old boy with Proteus syndrome. Note the generalized overgrowth, upper and lower limb length discrepancy, localized limb distortion of the left knee (A), postural flexion deformity of the left knee (B), and mild dorsal scoliotic deformity (C).

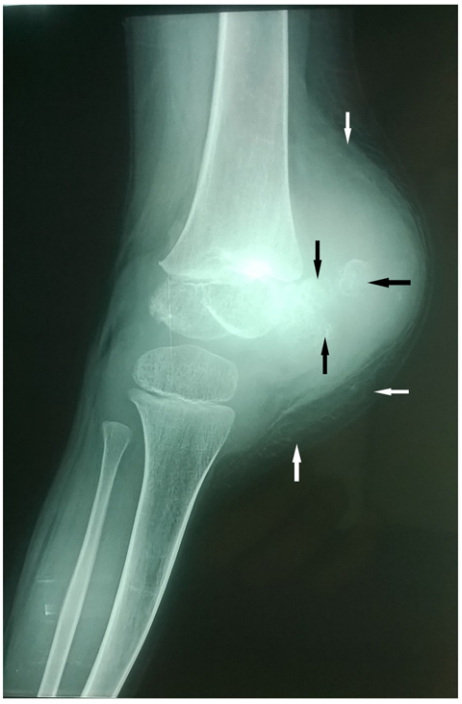

Fig. 3. Plain radiographs of the left knee, lateral view. Note the increased soft tissue shadow (white arrows) and para patellar hyperostosis (black arrows).

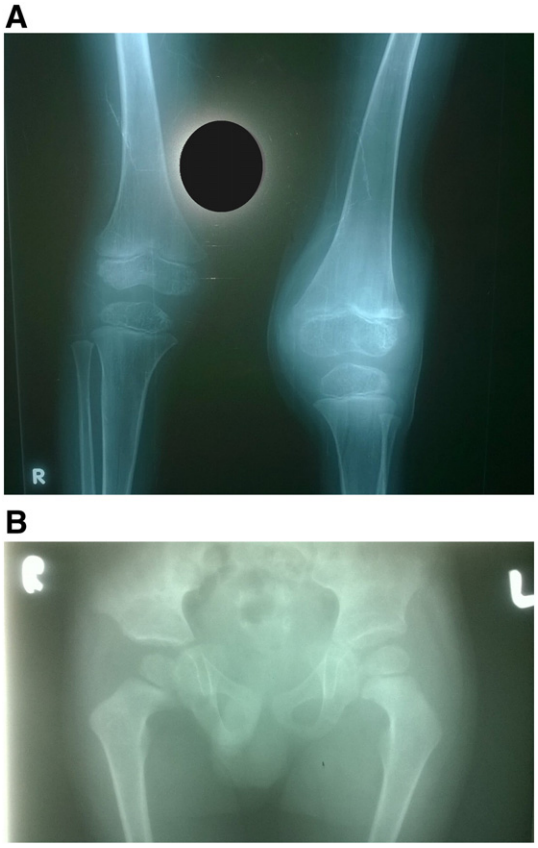

Fig. 5. (A, B): Anteroposterior radiographs of both knees (A) pelvis and both hips (B) demonstrating left para patellar hyperostosis. Note the relatively normal contour of the involved bones around the knees and hips.

distribution of the phenotype that occurs sporadically and that the manifestations are progressive in nature. If a patient has all three of these general attributes, the specific criteria are to be assessed (Biesecker, 2006). The reported manifestations of our patient met these PS diagnostic criteria. Our patient met all general criteria and category A of the specific criteria, namely the cerebriform connective tissue nevi that was sufficient to establish the diagnosis of PS. Moreover, various specific criteria of category B and C were also met: namely, asymmetric, disproportionate overgrowth of the limbs, hyperostosis of the skull, lipomas, facial phenotypic features such as dolichocephaly, long face, open mouth at rest and low nasal bridge.

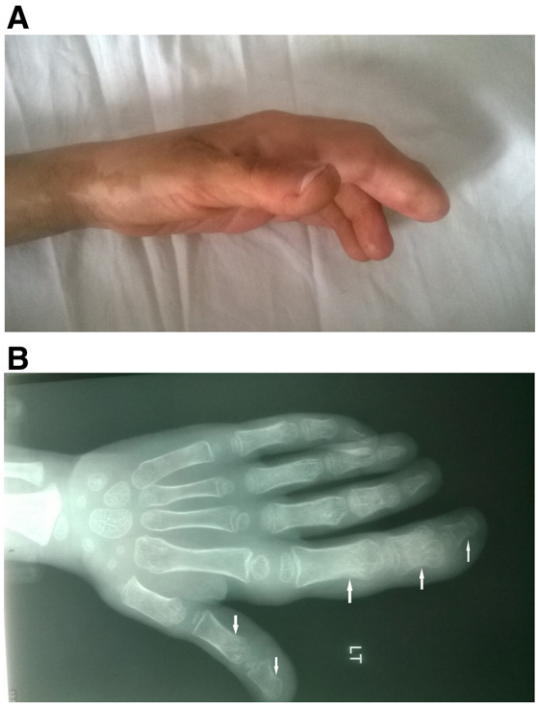

Fig. 4. (A, B): Macrodactyly of the left index and thumb. Note the finger distortion (A), and retained shape and contour of the enlarged bones of the first and second ray (B).

The ratio of males to females among reported cases of PS who meet the diagnostic criteria is 1.9:1 (Turner et al., 2004). This also goes in line with our male patient. The diagnostic criteria may have important clinical and research utility. In clinical practice, it is helpful for clinicians to be aware of severe and relentless overgrowth and likelihood of serious complications in patients who meet the diagnostic criteria of PS. Moreover, the literature has more reports of patients misdiagnosed than correctly diagnosed. Only 47.3% of reported cases in literature met the diagnostic criteria for PS (Biesecker, 2006; Turner et al., 2004). This may be attributed to inconsistent application of diagnostic criteria. Furthermore, these criteria were published after many case reports appeared in the literature (Biesecker, 2006; Turner et al., 2004). In our reported case, the diagnosis of PS was based on adequate clinical data and strict application of revised diagnostic criteria. We, therefore, believe that our reported case of PS has a significant clinical and research utility, in contrast to other published cases that have been suggestively labelled or mislabelled as PS.

PS is distinguished by the presence of irregular and disorganized bone, including hyperostosis, hyper-proliferation of osteoid with variable calcification causing abnormal bony edges, abnormally calcified connective tissue, and invasion of joint spaces, which frequently result in joint immobility (Biesecker, 2006). These findings correlated to the findings of our patient, especially around the left knee. Nevertheless, our patient exhibited a full range of motion of the knee.

Jamis-Dow et al. (2004) studied the radiological manifestations of PS using the diagnostic criteria proposed by Biesecker (2006). They

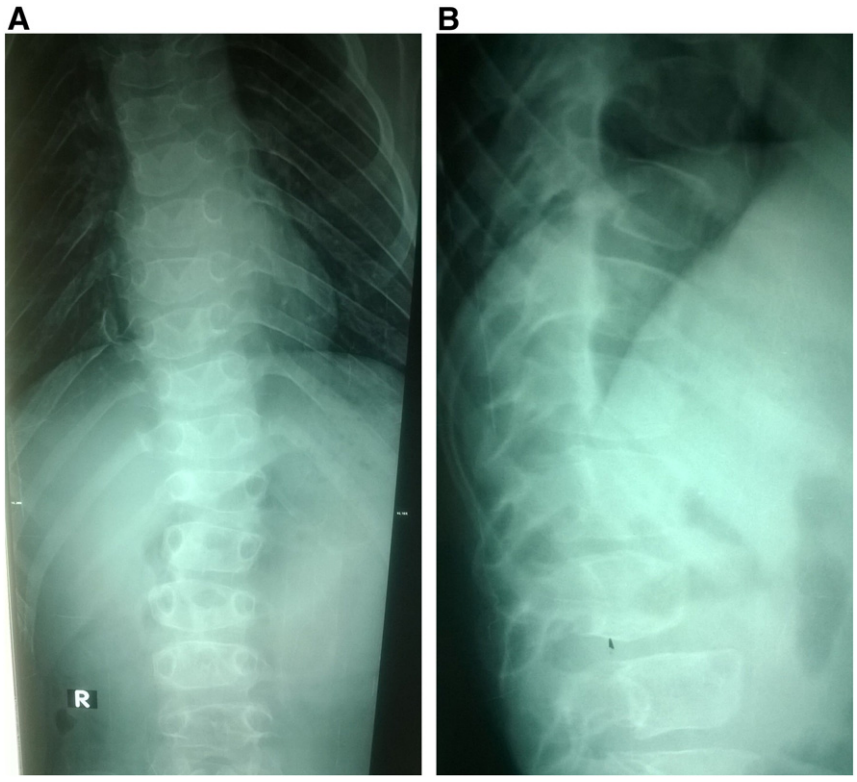

Fig. 6. (A, B): Anteroposterior view (A) and lateral view (B) of the dorsal spine. Note the presence of abnormal vertebrae in both views and mild scoliotic curve to the left (A) and distorted sagittal alignment (B).

observed that macrodactyly, asymmetric overgrowth, and limb length discrepancy are the most frequent and striking findings in patients with PS (Jamis-Dow et al., 2004). Sticker reviewed the available literature and he found 61 patients with orthopaedic problems related to PS and reported similar findings, in addition to knee valgus and hyperostosis of foot bones (Sticker, 1992). Furthermore, similar observations were reported (Kim, 2014; Kaduthodil et al., 2012; Biesecker et al., 1999). There was an agreement between the previous authors and the findings reported in our patient. It is not unusual for a child with PS to develop a leg-length discrepancy of greater than 10 cm before the age of 10 years (Tosi et al., 2011). The reported lower limb-length discrepancy of our patient was 7 cm.

In PS, the hands are also frequently involved, with significant functional compromise. The shoulders and elbows, by contrast, are rarely involved (Tosi et al., 2011). These findings go in line with the pattern of upper limb joint involvement in our patient. Nevertheless, our patient was not functionally compromised, a matter to be probably attributed to the young age of our patient.

It has been reported that most characteristic findings in PS are the disorganization and distortion of skeletal features, which contrast strikingly with more common forms of osseous overgrowth in which the enlarged bones retain their normal proportional relationships (Biesecker, 2006; Jamis-Dow et al., 2004). In contrast, Tosi et al. (2011)) and Kim (2014)) reported that patients with PS could also have enlarged bones with a generally normal shape and contour. The skeletal abnormalities in our patient affirm the observations of both previous studies (Kim, 2014; Tosi et al., 2011).

Scoliosis is a common manifestation of PS (Jamis-Dow et al., 2004; Sticker, 1992; Kim, 2014; Kaduthodil et al., 2012; Biesecker et al., 1999; Tosi et al., 2011). The time of onset of scoliosis in PS is similar to that of adolescent idiopathic scoliosis (Tosi et al., 2011). In contrast, our 5 year old patient demonstrated a mild dorsal scoliotic deformity. Nevertheless, our case depicted dysmorphic and asymmetric vertebral bodies on plain radiographs, a finding that was shared by many authors (Jamis-Dow et al., 2004; Sticker, 1992; Kaduthodil et al., 2012; Biesecker et al., 1999; Tosi et al., 2011).

4. Conclusion

Review of available literature shows that there tends to be a highly characteristic pattern of skeletal abnormalities in PS. Due to the rarity of PS, occurrence of other syndromes with overlapping clinical manifestations and lack of genetic tests for diagnosis, clinical and radiographic examinations are important contributors to the diagnosis. The present case reinforces the need for supplementary musculoskeletal imaging modalities to be implemented in the diagnosis. Effective management requires an integrated multidisciplinary approach. The clinical utility of the reported cases is significantly dependent on consistent application of diagnostic criteria that augment diagnostic accuracy.

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