Diagn Interv Radiol 2013; 19:240–243

PEDIATRIC RADIOLOGY
CASE REPORT

Proteus syndrome: a case report with bone scintigraphy findings

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ABSTRACT
Proteus syndrome is an extremely rare genetic disorder characterized by an asymmetrical overgrowth of skin, bones, muscles, fatty tissues, and blood and lymphatic vessels. We present a case of a six-year-old boy with proteus syndrome who underwent bone scintigraphy for suspected osteomyelitis. Bone scintigraphy ruled out osteomyelitis and suggested cellulitis. In addition, it demonstrated striking characteristic deformities, which need to be emphasized. Knowledge of these findings will avoid misinterpretation of bone scintigraphy in patients with proteus syndrome.

Proteus syndrome (PS) is a rare, complex, progressive, and disfiguring disorder that manifests variably as asymmetric, disproportionate overgrowth of body tissues derived from any germline layer. Although Cohen and Hayden (1) first described the disease in 1979, the term "proteus syndrome" was coined by Wiedemann et al. (2) in 1983 after Proteus, the Greek god, who could take any form. This exceedingly rare syndrome affecting less than one per million does not recur in affected families, and has been found to affect only one sibling in the case of monozygotic twins. Almost three decades after Cohen and Hayden first described the syndrome, Lindhurst et al. (3) identified the somatic activating mutation in serine-threonine protein kinase AKT1 responsible for the disease. Due to the multitude of variability in the presentation and the rarity of the disease, misdiagnosis is not uncommon.

We present a case of PS in a non-Asian Indian boy along with the bone scintigraphy findings. Bone scintigraphy is not routinely indicated in the work up of these patients, however the predominant involvement of the skeletal system might imply the necessity of bone scintigraphy in selected cases. Also, physicians should have a working knowledge of the bone scintigraphy findings of this rare condition to prevent possible misinterpretation and misdiagnosis.

Case report

This six-year-old non-Asian Indian male child was born to non-consanguineous parents by full-term normal vaginal institutional delivery. There was no history of similar illness in the family. The boy had a history of neonatal jaundice that required phototherapy. At birth, he was found to have multiple morphological deformities. Gradually, the child became progressively anemic, and on evaluation was found to have multiple gastrointestinal hemangiomas. Due to progressive anemia, he received frequent blood transfusions every six to seven months. The patient also developed a subcutaneous swelling on the back, which was confirmed to be a lipoma on biopsy. The deformities due to asymmetric overgrowth of head, limbs, fingers, and toes also increased over time, and he was clinically diagnosed as PS at four years of age. Since no genetic testing was available to diagnose PS, genetic analysis could not be performed.

The patient presented to our institute with six days history of high grade fever with progressive swelling of the left shoulder extending up to the forearm and anterior part of chest, along with erythema and scaling. On examination, he had striking deformities: facial asymmetry, enlarged left upper limb, and enlarged and curved left middle finger, left first four toes, and right second to fourth toes (Fig. 1). Written informed

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Received 5 October 2012; accepted 26 October 2012

Published online 16 Jaunary 2013
DOI 10.5152/dir.2013.081

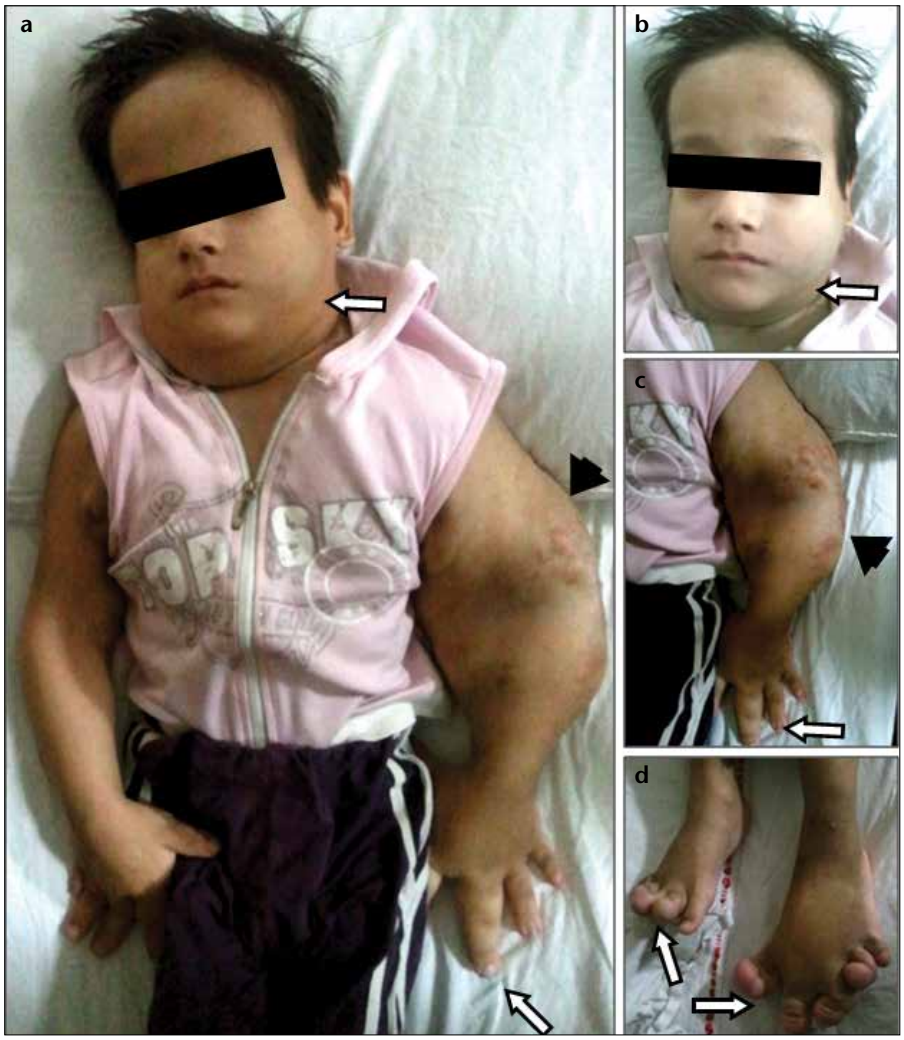

Figure 1. a–d. A six-year-old non-Asian Indian boy with Proteus syndrome. Features include typical facial phenotype; asymmetric, disproportionate, and progressive overgrowth of all the four limbs; lipoma at the back of the trunk (not seen in the picture); macrodactyly with abnormal bending of the digits of hands and feet (*white arrows*) **(a–d)**. The left upper and lower limbs are affected more than the corresponding right counterparts. Patient presented with a recent history of progressive swelling of the left shoulder extending to the left chest, left arm and forearm, along with fever. The swelling was tender and hot on touch with scaling, erythema, and serosanguinous discharge from the overlying skin (*black arrows*) **(a, c)**.

consent was obtained from the parents for the use of identifiable photographs. There was no neurological deficit. The shoulder swelling was tender and hot on touch, and there was serosanguinous discharge. Visible veins were also noted over the swollen chest on the left. Routine blood examination revealed leukocytosis and anemia.

To rule out possible osteomyelitis of the underling bones, bone scintigraphy was advised. Three-phase bone scintigraphy with ^{99m}Tc-methylene diphosphonate did not reveal any features suggestive of osteomyelitis. However, there was mildly increased flow and pool activity in the region of left arm (Fig. 2a and 2b) with no abnormally increased tracer uptake in the underlying bone on delayed static image (Fig. 2). These features were suggestive of soft tissue inflammation/infection, and the patient was managed conservatively. Apart from this, there were striking characteristic findings on the bone scintigraphy, which need to be emphasized (Fig. 2).

Discussion

Because of the rarity of the condition, little is known regarding the natural history of PS, and misdiagnosis for other dysmorphic conditions is not uncommon. Happle (4) originally postulated the cause of PS to be a mosaic somatic mutation that is lethal in the constitutive state. However, the causative gene could not be mapped for decades until very recently, when Lindhurst et al. (3) found a mosaic activating mutation in AKT1 by exome sequencing of DNA and a phosphorylation-specific antibody assay in 158 biopsy samples from 29 patients. The landmark discovery has opened a new horizon for better understanding of the condition and possible targeted gene therapy in the future. As of now, no genetic testing is available for the diagnosis of PS, so a tactical multidisciplinary approach is needed for the diagnosis and management of the condition.

Important differential diagnoses include Klippel-Trenaunay syndrome, Parkes Weber syndrome, Maffucci syndrome, neurofibromatosis (Type-1), epidermal nevus syndrome, Bannayan-Riley-Ruvalcaba syndrome, hemihyperplasia/lipomatosis syndrome, familial lipomatosis, symmetrical lipomatosis, and encephalocraniocutaneous lipomatosis. To avoid diagnostic confusion, Biesecker et al. (5) published diagnostic criteria and guidelines for patient evaluation. Many case reports published before and after the development of the diagnostic criteria included individuals who were affected by other overgrowth conditions, rather than PS. To address the issue of misdiagnosis, Turner et al. (6) re-emphasized the diagnostic criteria with revisions. Our patient satisfies the diagnostic criteria laid by Biesecker et al. (5).

Causes of premature death in PS include pulmonary embolism, postoperative complications, and pneumonia. Health care providers should be aware of the risk of deep vein thrombosis and pulmonary embolism. In addition, patients undergoing surgical procedures should be evaluated by a hematologist for proper management if coagulopathy is established (7).

The PS most commonly affects the skeleton. Various radiological findings have been described, which include macrodactyly, clinodactyly, asymmetric overgrowth of limbs, abnormal vertebral bodies, scoliosis, hyperostosis, focal calvarial thickening, rib abnor-

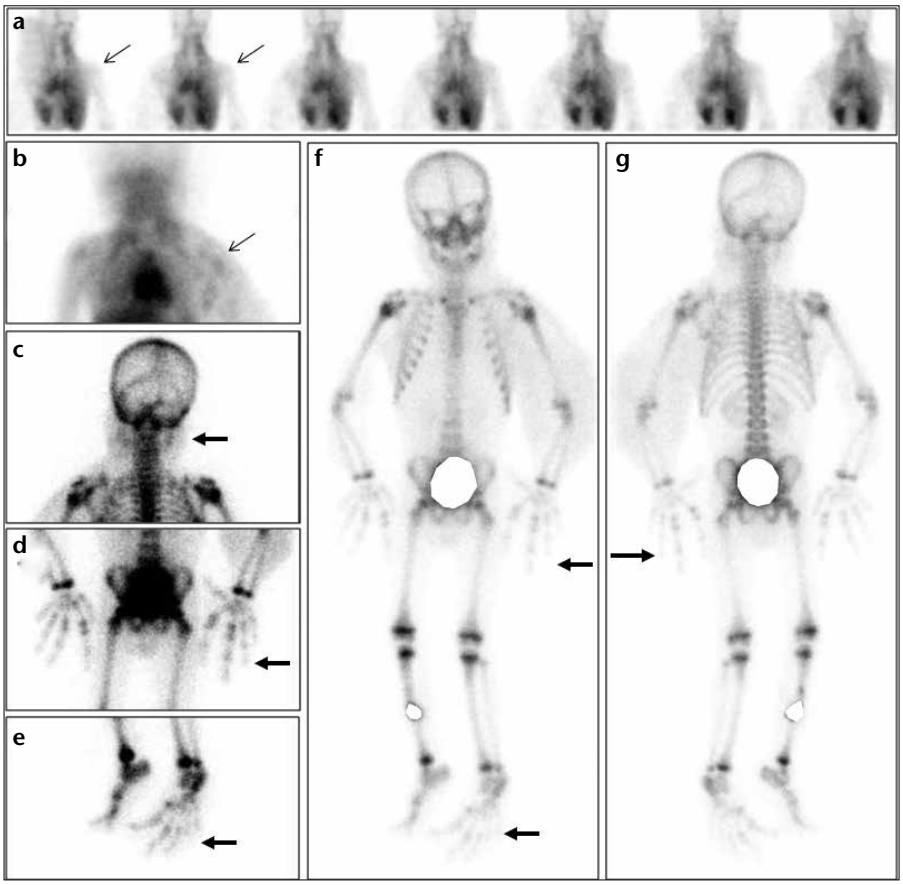

Figure 2. a–g. Three-phase bone scintigraphy performed with ^{99m}Tc-methylene diphosphonate reveals increased flow and pool activity in the region of the left shoulder and adjoining upper arm **(a, b,** *arrows***)**. On delayed whole body static images **(c–g),** there is no abnormal tracer uptake in the underlying bones in this region (*arrows*). Findings were suggestive of inflammation/infection of the soft tissues. Apart from this, there are striking features of Proteus syndrome. Prominent soft tissue outline is noted in the submandibular and neck regions **(c,** *arrow*), in the region of the left shoulder, left upper arm, and entire left forearm **(f, g,** *arrows*), consistent with soft tissue overgrowth. Another striking finding is digital gigantism (macrodactyly) involving both hands **(d,** *arrow*) and bilateral feet **(e,** *arrow*), which is more marked in the left. Also note the increased tracer uptake in the region of epiphseal plates, normally seen in growing children. This is important if epiphysiodesis for limb discrepancy correction is considered.

malities, and discordant bone age (8). Findings on bone scintigraphy can be confusing, and there is very little literature in this regard. Joshi et al. (9) reported PS as a rare cause of hemihypertrophy and macrodactyly on bone scanning. Rink et al. (10) used bone scintigraphy as a part of a work-up of a patient in differentiating between PS and Klippel-Trenaunay syndrome. In spite of these encouraging reports, bone scintigraphy is not routinely indicated in PS. As the disease invariably involves the skeleton, it might be indicated in selected cases, such as in differentiation of osteomyelitis from cellulitis (common due to ulceration and infection of the overlying skin and soft tissues), evaluation of epiphyseal activity for epiphyseodesis to correct limb length discrepancy, assessment of vascularity of vulnerable bones (due to continued growth of bone/other tissues or resultant pathological fracture causing vascular compromise), and so on. Moreover, due to the rarity of the disease and infrequent use of bone scintigraphy, radiologists might misinterpret the findings that are characteristic of this rare syndrome. Our patient was referred to rule out osteomyelitis. Three-phase bone scintigraphy ruled out osteomyelitis and suggested soft tissue inflammation/infection of the left arm. Apart from this, there were striking bone scintigraphy findings that were quite unusual and merit emphasis. Asymmetric, disproportionate growth/enlargement of multiple bones in a mosaic pattern along with macrodactyly involving two or more digits was a characteristic finding. This might be pathognomic of PS and need further evaluation.

In conclusion, little is known about PS, and its rare occurrence presents a challenge in better understanding the condition. The discovery of the somatic activating mutation of AKT1 as the cause has opened a new horizon for research with respect to elucidating the pathophysiology, diagnosis, and management of this rare condition. Use of bone scintigraphy in selected patients should not be underestimated. In addition to the ability of bone scintigraphy to rule out bone infection, our case report highlights the characteristic striking bone scan findings that could be very confusing to physicians unfamiliar with PS, which is often the case due to the rarity of the disease and infrequent use of bone scintigraphy. Physicians should have a working knowledge of these important findings that might be, at times, pathognomic of the condition.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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