Proteus syndrome: a case report with bone scintigraphy findings

Bangkim Chandra Khangembam, Sellam Karunanithi, Punit Sharma, Krishan Kant Agarwal, Abhinav Singhal, Varun Singh Dhull, Chandrasekhar Bal, Rakesh Kumar

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
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 underlying 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 the 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, asymmetrical overgrowth of limbs, abnormal vertebral bodies, scoliosis, hyperostosis, focal calvarial thickening, rib abnor-
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 epiphysial 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, disproportion-

