

Proteus syndrome: A rare cause of gigantic limb

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ABSTRACT

A congenital disorder with variable manifestations, including partial gigantism of the hands and feet with hypertrophy of soles, nevi, hemihypertrophy, gynecomastia, macrocephaly and other skull abnormalities, and abdominal lipomatosis. The cause is unknown, although a genetic origin, generally of autosomal-dominant transmission, has been conjectured. Symptoms can be treated, but there is no known cure. We present the case of a young male with grotesque overgrowth of the right lower limb, splenomegaly and multiple nevi. Angiography revealed venous malformation within the limb. The findings are in conformity to the criteria for the Proteus syndrome.

Key words: Gigantic limb, nevi, overgrowth, Proteus, venous malformation

INTRODUCTION

Proteus syndrome is a congenital disorder with a highly variable clinical spectrum. Characteristically, the patients are normal at birth but progressively develop the manifestations during childhood. The cause is largely unknown, but a genetic mutation that is viable only in a mosaic pattern, has been postulated. Germ line PTEN mutations have been implicated that predispose to phenotypically different disorders with considerable overlaps like Cowden syndrome, Bannayan Riley Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndromes.^[1-3]

CASE REPORT

An 18-year-old male undergraduate student, presented with disproportionate enlargement of right lower limb since 10 years of age [Figure 1], abdominal swelling for last 5 years and growth retardation. He was the first issue from a non-consanguineous marriage and had a normal delivery and normal initial growth spurt that slowed down with adolescence. Sibling history and family history were noncontributory. On examination patient was active and alert with normal higher mental function. However, he had an abnormal body habitus with kyphoscoliosis [Figure 2], left sided gynecomastia and gigantic overgrowth of

right lower limb including toes [Figure 3]. His left lower limb was comparatively atrophied. There were multiple nevi distributed predominantly over the right flank, buttock, and right leg with secondary edema, occasional exudation and eczematous skin changes in the whole of the right lower limb [Figures 1 and 4]. These epidermal nevi had a mosaic distribution without any cerebriform or gyriform malformation. Facial features were unremarkable. His sexual maturation rate was G3 P4 A2 (G-Genital maturity P-Pubic hair A-Axillary hair) and bone age (by radiograph of both wrist joints) corroborated with chronological age. There was no bruit anywhere in the gigantic limb. Patient had a huge splenomegaly (15 cm below the costal margin in its own axis), and the rest of his systemic examination findings were normal. USG abdomen showed massive splenomegaly. Chest radiograph, ECG, and other biochemical parameters were unremarkable. The peripheral blood picture revealed trilineage suppression, though bone marrow study was normal. This could be explained by hypersplenism. Upper GI endoscopy and Hb electrophoresis were within normal limits. Femoral angiography done elsewhere, revealed only venous malformation.

At this juncture our differential diagnosis revolved around Klippel-Tre'nauay syndrome, Proteus syndrome, Parkes Weber syndrome, Neurofibromatosis type 1, and

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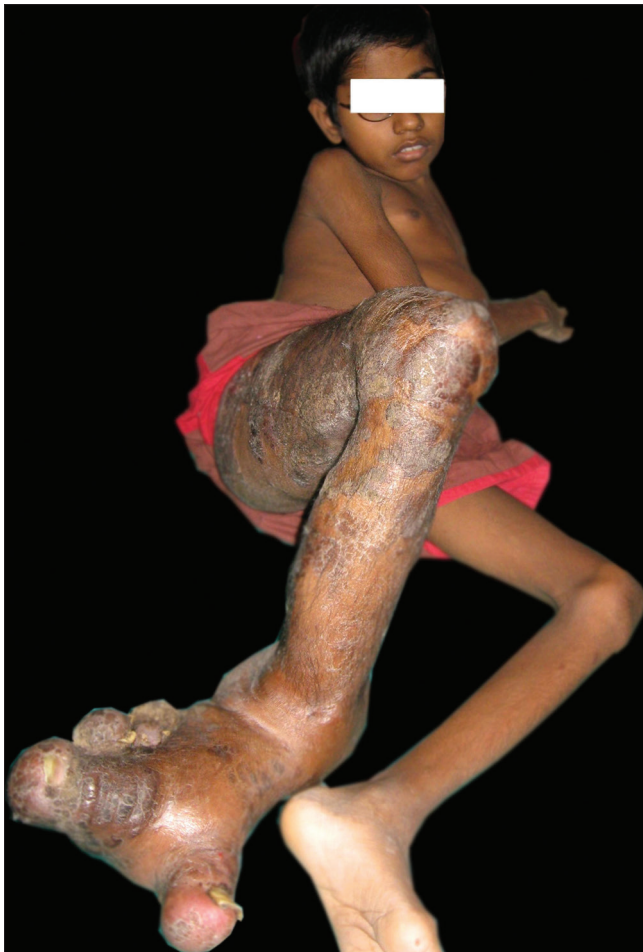


Figure 1: Disproportionate enlargement of right lower limb with epidermal nevi

Hemihyperplasia-multiple lipomatosis syndrome. The last two were ruled out by absence of stigmata of neurofibroma or lipoma. Among the rest, Klippel-Tre'nauay is a condition of slow flow, mixed capillary venous and lymphatic malformation, commonly severe and present since birth in contrast to Proteus syndrome which presents at a much later age. Parkes Weber syndrome is a fast flow, vascular malformation of upper/lower limbs, characterized by diffuse, often confluent, capillary blush, warmth, and underlying arteriovenous shunts. However, this patient had only venous malformations with no arterial involvement.

DISCUSSION

Proteus syndrome, named after the Greek God Proteus, who could change His shape at will, is a complex disorder comprising malformations and overgrowth of multiple tissues. Proteus syndrome, is also known as Wiedemann syndrome after the German pediatrician.

It is believed to be exceedingly rare, with about 100-200 cases



Figure 2: Abnormal body habitus with kyphoscoliosis

reported worldwide suggesting a prevalence of less than 1 per 1,000,000 live births.

It is highly variable and conspicuous by its mosaic distribution. Lindhurst *et al.*, identified an activating mutation in AKT1 kinase in a mosaic state gene. A single-nucleotide polymorphism in this gene causes Proteus syndrome.^[4]

There are three mandatory diagnostic criteria of Proteus syndrome which includes (a) mosaic distribution of lesions, (b) lesions follow a progressive course, and (c) condition appears to be sporadic in nature. Categories of confirmatory diagnostic criteria are as follows.^[5]

A (1 required) - Connective tissue nevus

B (2 required)

- Epidermal nevus
- Disproportionate overgrowth of 1 or more of the following: Limbs, digits, cranium, vertebrae, external auditory meatus, spleen, or thymus
- Ovarian cyst adenomas or a parotid adenoma in a patient younger than 20 years.

C (all 3 required)

- Lipomas or focal atrophy of adipose tissue



Figure 3: Unilateral gynecomastia

- Capillary, venous, or lymphatic malformation
- Facial features including dolichocephaly, a long face, down-slanting palpebrae, ptosis, depressed nasal bridge, anteverted nares, and open mouth position while at rest.

This patient fulfilled all the mandatory criteria and first two of the specific diagnostic criteria in category B to be diagnosed as Proteus syndrome. He had disproportionate growth of one limb and digits, multiple epidermal nevi and splenomegaly. Visceral involvement is less common than musculoskeletal or soft tissue abnormalities. In a radiological series with 21 patients, 29% patients had visceromegaly. Other organs involved were kidney and brain. Vascular malformations were reported in seven out of the 21 patients. In a series of 18 surgical specimens, histopathology revealed increased amounts of disorganized tissue, indicating hamartomatous type defects in which normal tissues were present in abnormal distribution and architecture^{6,7} The main concern was risk of premature death due to deep vein thrombosis and pulmonary embolism caused by the vessel malformations that are associated with this disorder. Also, in view of the relentless disproportionate growth, total disfigurement and risk of future malignant transformation (less than 5%), our patient underwent amputation of the right lower limb with disarticulation at hip joint to achieve maximum attainable function. Post-operative period was uneventful.



Figure 4: Capillary (Verrucous) hemangioma on the thigh and flank

The histopathology of amputated tissue showed partial lipohyperplasia with venous malformations. Patient is on regular follow-up without any complications. Although the antiproliferative effects of sirolimus (Rapamycin) is said to have a role in treating Proteus syndrome, our patient presented in a very advanced state and could not afford such therapy.

REFERENCES

1. Orloff MS, Eng C. Genetic and phenotypic heterogeneity in the PTEN Hamartoma Tumour Syndrome. *Oncogene* 2008;27:5387-97.
2. Lyons K, Ezaki M, Molecular regulation of limb growth. *J Bone Joint Surg Am* 2009;91:47-52.
3. Biesecker L. The challenges of Proteus syndrome: Diagnosis and management. *Eur J Hum Genet* 2006;14:1151-7.
4. Lindhurst MJ, Sapp JC, Janie K, Johnston JJ, Finn EM, Peters K, et al. A mosaic Activating Mutation in AKT1 Associated with the Proteus Syndrome. *N Engl J Med* 2011;365:7
5. Hamm H. Cutaneous mosaicism of lethal mutations. *Am J Med Genet* 1999;85:342-5.
6. Biesecker LG, Happle R, Mulliken JB, Weksberg R, Graham JM Jr, Viljoen DL, et al. Proteus Syndrome: Diagnostic Criteria, Differential Diagnosis, and Patient Evaluation. *American Journal of Medical Genetics* 1999;84:389-95.
7. Jamis-Dow CA, Turner J, Biesecker LG, Choyke PL. Radiologic manifestations of Proteus Syndrome. *Radiographics* 2004;24:1051-68.

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