

Proteus Syndrome: Case Report from Karachi, Pakistan

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Introduction

Proteus Syndrome (PS) is a rare disorder which includes malformations and excessive growth of many tissues. The prevalence of PS has been estimated to be less than 1 case per 1,000,000 live births [1]. It is described as asymmetric disproportionate enlargement of skull, limbs or vertebra, with multiple of cutaneous lesions. A pathognomonic feature of PS is cerebriform connective tissue nevi, esp. of plantar foot, albeit it has not been reported in many cases [2].

The term Proteus Syndrome was first coined by Wiedemann et al in 1983, after the Greek God Proteus who displayed multiple forms [3]. Turner et al conducted a detailed literature review in 2004, and found about 205 case reports published on PS till then [4]. They further reported that out of those 205 cases, only 97 were true cases of PS based on the diagnostic criteria. The syndrome can occur in any race, and is slightly predominant in males with a male to female ratio of 1.9:1 [4].

In Pakistan, Mashood et al reported a case of PS in 2007 [5]. Our case is the second confirmed case ever reported from Pakistan. The aim of our report is to contribute to the literature about the presentation, diagnosis and management of PS syndrome.

Case Report

18 year old, unmarried male presented in out-patient department with complaint of unilateral right leg and thigh swelling since birth. It has gradually progressed over years to the present size. It is associated with increase size of hands and feet. There is no history of similar illness in family.

On examination, the patient is noted to have nasal twang with high arched palate. Patient had normal intelligence and his vital were stable. He had epidermal naevus present over the back of neck, face, forehead and upper chest with easy bruisability. His hand and feet were enlarged bilaterally. The right leg had unilateral non-pitting edema below knee. Multiple dilated veins were visible on medial and lateral side of both legs but more prominent on medial side. Patient had saphenavarix, with a positive cough impulse. The Schawartz and Fagan test were positive but modified Perthe's was negative. Patient's had syndactyly of second and third toe of right foot. The other systemic examination was unremarkable (Figures 1-4).



Figure 1: Epidermal nevus seen on right side of neck.

On investigation, complete blood count, blood urea nitrogen, electrolytes, creatinine and coagulation profile were within normal limits. The chest radiograph was normal.



Figure 2: varicose vein seen on lower limb.



Figure 3: Syndactyly present between second and third toes of right feet.

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Figure 4: Enlargement of bones and soft tissues.

Doppler U/S

Ultrasound Doppler of both legs showed bilateral varicose vein with dilated and incompetent perforators and with incompetent sphenofemoral and sphenopopiteal junction. Impending deep venous thrombosis in right and left common femoral vein was shown with slow flow and internal echoes.

Radiographical Finding

Radiograph of ankles of both the limbs shows increase abnormal soft tissues swelling around distal phalanges with subluxation of second and third distal inter phalangeal joints. Overhanging margin in first distal inter phalangeal joint with reduced joint space of both middle and distal inter phalangeal joints was also seen.

Histopathological Report

A skin biopsy was performed on one the lesion suspected to be epidermal nevus and histopathology report confirm the diagnosis.

We have advised the patient to wear compression stocking grade 2 and tablet Ascard 75 mg one tablet daily. No surgical intervention was required for this patient.

Discussion

The cause of Proteus syndrome is unknown, although various hypotheses have been postulated. According to Lindhurst et al, mosaic activating c.49G>A.pGlu27lys AK1 mutation was the cause of Proteus Syndrome [6].

Main clinical presentation of Proteus syndrome include asymmetrical and disproportionate overgrowth of various tissue such as limbs, especially the lower limb, skull and viscera, cerebriform connective tissue nevi, epidermal nevi, vascular malformations and facial dysmorphism. Overgrowth is patchy which may be seen early after birth. However, presentation is highly variable and no diagnostic test has been developed, which usually leads to misdiagnosis. The following three general characteristics or features are believed to be mandatory to make a diagnosis.

- i. Lesion must have a mosaic distribution.
- ii. Follow a progressive course.
- iii. Inherited in sporadic fashion

In addition to above mentioned general characteristics, special characteristics are grouped into three categories: A, B and C. A diagnosis of Proteus syndrome requires all three general features to be

present and either one feature from Category A, or two features from Category B, or three features from Category C. These features are listed in the Table 1.

Other common finding include ophthalmologic abnormalities (42%), CNS include mental retardation (40%), cystic lung malformation (12-13%) and urological abnormalities (9%).

The most prominent feature of Proteus syndrome is macrodactyly which may also be present as macrosyndactyly [7]. Skin abnormalities in Proteus syndrome include cerebriform connective tissue nevi, epidermal nevi, vascular malformation, lipomas, lipohypoplasia, and dermal hypoplasia. Patient with greater number of skin abnormalities tended to have greater number of extra cutaneous abnormalities. Number of abnormalities tends to increase with age up to 8 years [8]. Vascular anomalies also occur characterized by a triad of anomalous veins, portwine stains and enlargement of limbs. Overgrowth in Proteus syndrome is progressive and can be difficult to manage.

Various syndromes are considered in differential diagnosis of Proteus syndrome which is listed in Table 2. Two most common disorders confused with Proteus syndrome are hemihyperplasia/lipomatosis syndrome and Klippel-Trenaunay syndrome. Hemihyperplasia with multiple lipomas is distinct set of hemihyperplasia. Mild to moderate

S.No	Criteria
General Criteria	
1	Mosaic distribution Progressive course Sporadic occurrence
Specific Criteria	
2	Category A Cerebriform connective tissue nevus
3	Category B Linear epidermal nevus Asymmetric, disproportionate overgrowth of two of: Limbs, skull, external auditory canal, vertebrae, or viscera Specific tumors in the first decade of life: Bilateral ovarian cystadenomas Monomorphic parotid adenomas
4	Category C Dysregulated adipose tissue Vascular Malformations Capillary, venous, and/or lymphatic Lung bullae Facial phenotype: Long face, dolichocephaly, down-slanted palpebral fissures, low nasal bridge, wide or anteverted nares open mouth at rest.
The diagnosis of Proteus syndrome requires all three general criteria, Plus one criterion from category A, or two criteria from category B, three criteria from category C. (Adapted from Biesecker, 2006)	

Table 1: General characteristics and special characteristics.

S.No	Differential Diagnosis
1	Klippel-Trenaunay syndrome
2	Parkes Weber syndrome
3	Maffucci syndrome
4	Neurofibromatosis, type 1
5	Bannayan-Riley-Ruvalcaba syndrome
6	Hemihyperplasia/lipomatosis syndrome
7	Familial lipomatosis
8	Symmetrical lipomatosis
9	Encephalocraniocutaneous lipomatosis

Table 2: Differential diagnosis of proteus syndrome.

signs are present at birth which tends to commensurate with growth of the child. Progressive overgrowth does not occur in hemihyperplasia/lipomatosis syndrome. In Klippel-trenaunay syndrome, traid of portwine stain, varicose vein and bony soft tissue hypertrophy of extremity are seen.

Each patient diagnosed with Proteus syndrome will have individualized treatment due to different medical needs. Many patients with Proteus syndrome are followed by geneticist or another doctor, such as a pediatrician (for children) or internist (for adult) who coordinates their medical care. Rarely, Proteus syndrome requires aggressive or frequent treatment. In some cases, a particular feature of Proteus syndrome may be monitored over a period of time before a treatment decision is made. Many patients with Proteus syndrome are followed by an orthopedic surgeon for their bone problems. Dermatologist, physiatrist, pulmonologist, occupational therapist and a pedorthist might also be involved in treatment of Proteus syndrome patients.

Most common causes of death for patients with Proteus syndrome is deep venous thrombosis and pulmonary embolism, even in younger children. For this reason, it is strongly recommended that all patients who need to be operated for complication related to Proteus syndrome should undergo anticoagulant prophylaxis preoperatively [9]. Routine imaging surveillance for tumor is not recommended, however regular check up with physician who has relatively low threshold for ordering an appropriate evaluation if patients develops sign/symptom of tumor.

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