Proteus Syndrome

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Proteus syndrome (PS) is a rare complex disorder that produces a multifocal overgrowth of tissue in multiple systems [1]. The name was coined in 1983 by Wiedemann et al [2] after the Greek mythological god of the sea, Proteus, who was capable of changing his shape and form at will in order to avoid capture. It is thought that Joseph Merrick, an Englishman who lived in the late 19th century and became the subject of the 1980 American historical drama film "The Elephant Man", had the PS [3].

Fig 1A-E shows the images of a one-year-old male reported with a history of having been born with a congenital abnormality of both lower limbs. Antenatal history was normal and birth had occurred at full term normally after a non-consanguineous marriage. There was no family of congenital anomalies or chronic disorders. On examination, the feet were asymmetrically overgrown as compared to rest of the body and there was wide cutaneous hemangioma over the lateral side of both lower limbs, predominantly over thighs. Clinical examination and imaging survey of rest of the body did not reveal any apparent abnormality. The patient was referred to the tertiary care center for specialized care where the diagnosis of PS was established.

Progress has been made in understanding the etiology of PS in recent years, and there is evidence that it occurs after mutation (c.49G→A, p.Glu17Lys) of a somatic gene, named AKT1 oncogene [3-5]. This mutation is found in 90% of cases that satisfy the criteria for the diagnosis of PS. The AKT1 gene encodes the AKT1 kinase enzyme that plays important role in regulation of cell cycle (cell growth and division /proliferation and apoptosis). Cell lines with a mutation in AKT1 have been shown to display greater AKT phosphorylation that results in disruption of cell's ability to regulate its own growth resulting in abnormal growth and division [5]. AKT1 gene mutation is more common in groups of cells that experience overgrowth than in the cells that grow normally. PS is not, however, inherited, and there are no confirmed cases reported in the literature with the vertical transmission or sibling recurrence. On the basis of the molecular data, all affected cases are mosaic for the same AKT1 mutation (c.49G>A), indicating that the mutation occurs post-fertilization in one of the cells of a multicellular embryo. Hence other family members are not at increased risk nor do they require any evaluation.

There are several reports in literature that patients with PS had PTEN mutations [5]. But many other investigators have shown that persons with PTEN mutations were clinically distinct from those with PS and that patients with PS do not bear PTEN mutations [6,7].

Biesecker et al in 1999 presented criteria for the diagnosis of PS in an attempt to reduce the number of false clinical diagnoses of the syndrome [8]. These criteria gained global acceptance and are widely used in clinical practice for the diagnosis of PS. The diagnosis requires the presence of three general criteria and the presence of single criteria from category A or two from category B or three from category C as shown in Table 1.

AKT1 testing should be offered to all patients that meet the criteria necessary for the clinical diagnosis of Proteus syndrome. Ideally, a punch biopsy of affected tissue should be obtained and studied, but a skin scraping of epidermal nevi has also been noted to be effective [9].

Peripheral blood testing is not high yield in diagnosis due to the somatic nature of the mutation. To establish the extent of disease in an individual diagnosed with Proteus syndrome, detailed evaluations are recommended that include pulmonary function testing, skeletal survey, computed tomography, Magnetic Resonance Imaging, and Ultrasound [10].

The differential diagnosis of PS includes:

- Klippel-Trenaunay syndrome
- Encephalocraniocutaneouslipomatosis
- Hemihyperplasialipomatosis syndrome
- PTEN hamartoma tumor syndrome (PHTS)
- Vascular malformations
- Epidermal nevi (CLOVE) syndrome
- Congenital lipomatous overgrowth

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Figures A-B showing disproportionate growth of feet; **Figure C** showing the plane X-ray image of both feet depicting soft tissue overgrowth; **Figure D** showing hemangioma involving the lateral surface of left lower limb ; **Figure E** Magnetic resonance imaging of lower limbs with coronal T1-weighted sequences, showing soft tissue overgrowth in both feet and features of hemangioma in lateral things and legs

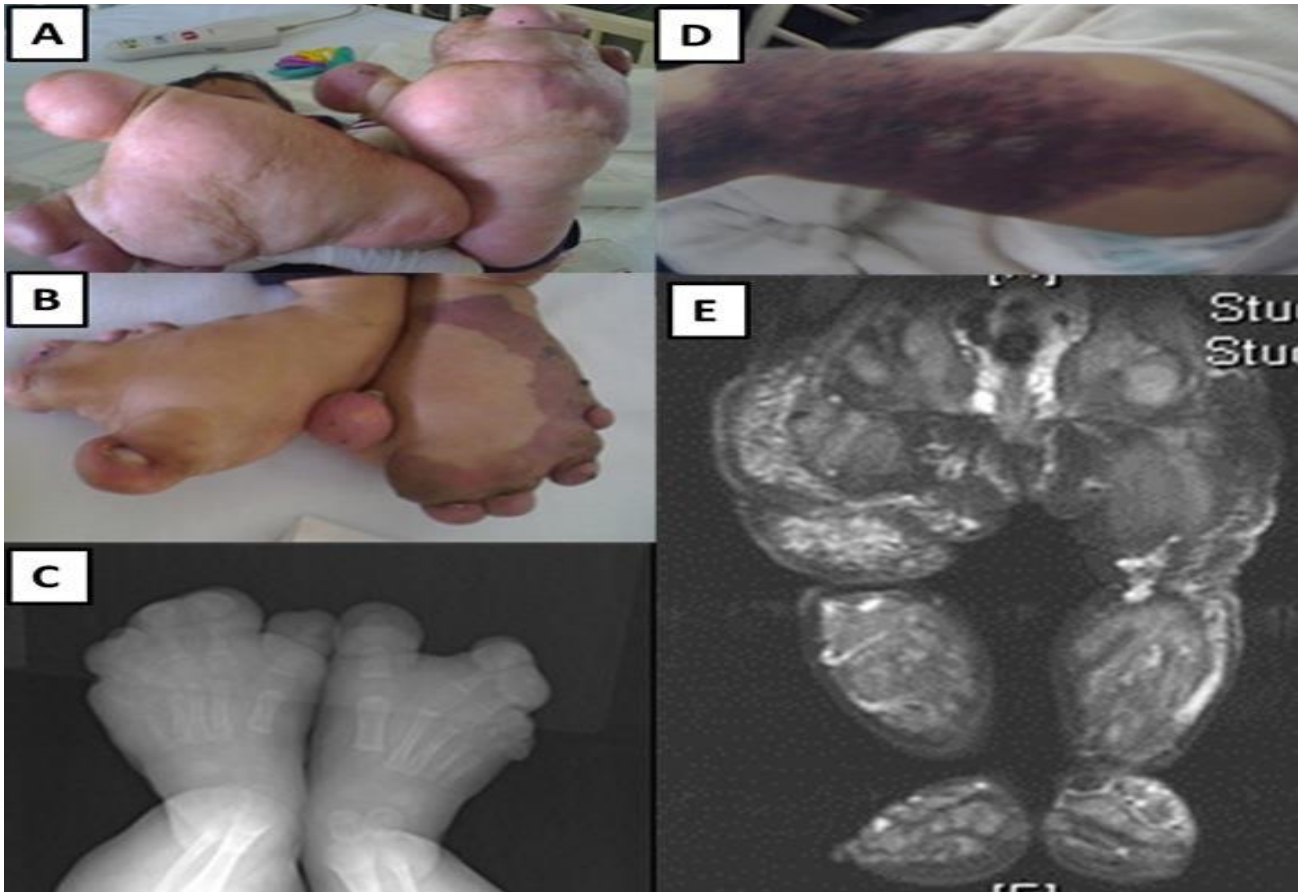

Table 1: Criteria for Diagnosis of Proteus Syndrome

Three general criteria necessary for establishing clinical diagnosis without regard to specific clinical features: I. Lesions follow a mosaic distribution or pattern II. Problems follow a progressive course III. The disorder appears to be sporadic (i.e., not inherited)
Category A I. Cerebriform connective tissue nevus
Category B I. Linear epidermal nevus; II. Disproportionate overgrowth of at least one the following: limbs, digits, cranium, vertebrae, external auditory meatus, spleen, or thymus and bilateral III. Ovarian cystadenomas or a parotid monomorphic adenoma in a patient younger than 20 years and
Category C I. Lipomas or Regional lipohypoplasia II. One of the vascular malformations (Capillary, venous, or lymphatic malformation) or lung bullae III. Facial phenotype including dolichocephaly, a long face, down - slanting palpebrae, ptosis, depressed nasal bridge, anteverted nares, and open mouth position while at rest.

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