Proteus Syndrome : A Case Report

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Abstract

Proteus syndrome is a rare genetic disorder, characterized by partial gigantism of the hands and/or feet, asymmetry of the limbs, plantar hyperplasia, multiple hamartomatous subcutaneous tumors, hyperostoses, and long bone overgrowth. A one day old Thai male infant is reported with macrosomia, hemihypertrophy of the left side of the face and left leg, large feet, macrodactyly of toes, plantar hyperplasia, large subcutaneous mass with a violet-red surface over the left side of the chest wall and a large port-wine stain involving the lateral aspect of the right chest wall. The clinical findings, diagnostic criteria, differential diagnosis, and management of the Proteus syndrome are reviewed.

Key word : Proteus Syndrome, Case Report

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Proteus syndrome is a congenital hamartomatous disorder that involves excessive growth of many tissues, including epidermis, adipose tissue, and bone. It is characterized by partial gigantism of the hands and/or feet, hemihypertrophy, plantar hyperplasia, hemagiomas, lipomas, lymphagiomas, pigmented nevi, macrocephaly and long bone overgrowth[1,2]. The syndrome was first recognized as a distinct syndrome in 1979 by Cohen and Hayden [3] who reported 2 patients as "a newly recognized hamartomatous syndrome". In 1983, Wiedemann et al[4] described the same condition in 4 patients

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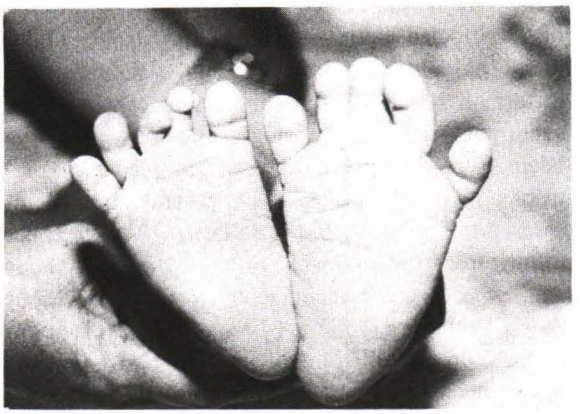

Fig. 1. Enlargement of feet and macrodactyly of the toes with early plantar cerebriform hyperplasia manifested as skin thickening and deep skin creases.

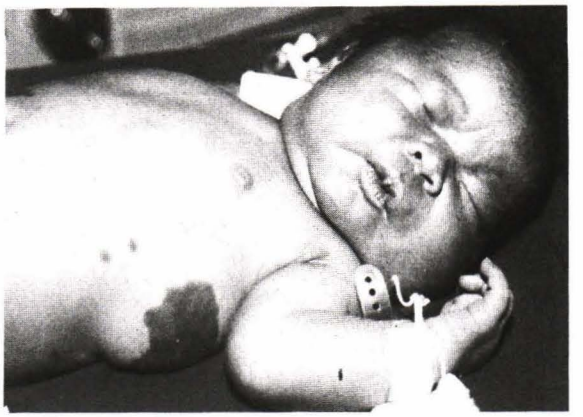

Fig. 2. Facial asymmetry due to hyperplasia of the left side. A soft subcutaneous mass, overlying a violet-red surface, is seen below the left axillary region.

and gave the name Proteus syndrome after the Greek god Proteus who could change his shape into different forms in order to avoid capture. Proteus syndrome is a rare genetic disorder. The incidence is less than 1 in 1,000,000 live births[5]. The cause of the disorder is unknown. Neither sex predilection nor advanced paternal age has been found[6]. More than 100 cases have now been reported in the literature[5,7]. This is the first case of Proteus syndrome reported in Thailand.

CASE REPORT

A one day old male infant was the product of a fullterm uncomplicated pregnancy delivered by cesarean section to a 31 year old $G_4 P_2 A_2$ mother. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. His mother had induced abortion in the first pregnancy and had spontaneous abortion in the third pregnancy. The parents were normal, consanguinity was denied and family history was unremarkable. An older sibling was healthy. The infant's birth weight was 5,400 g (> 90^{th} centile), length was 54.5 cm (> 90^{th} centile), and head circumference was 40 cm (> 90^{th} centile). Physical examination revealed a large-sized male infant with macrocephaly, epicanthal folds, marked facial asymmetry with hyperplasia of the left side, and overgrowth of the left leg. Both feet were gigantic with acrodactyly and plantar hyperplasia (Fig. 1). Below the left axilla, a large subcutaneous mass with a violet-red surface measuring 10 cm in diameter was noted (Fig. 2). A large port-wine stain involved the lateral aspect of the right chest wall. An undescended right testis was detected.

Laboratory investigation showed normal complete blood count, urinalysis, blood coagulation, BUN, creatinine, fasting blood sugar, and thyroid function tests. The ultrasonogram of the head and abdomen were also normal. The echocardiogram revealed a small PDA. Radiological studies showed enlargement of the phalanges of the deformed toes. Chromosome analysis by G-banding showed 46, XY.

DISCUSSION

Proteus syndrome is a rare congenital hamartomatous disorder that involves excessive growth of many tissues. In 1979, Cohen and Hayden[3] reported a newly discovered syndrome in 2 similar patients. Four years later, Wiedemann et al [4] described 4 patients with partial gigantism of the hands and/or feet, pigmented nevi, hemihypertrophy, subcutaneous hamartomatous tumors and macrocephaly, and/or other skull anomalies and proposed the term "Proteus syrdrome". Since then, a number of similar cases have been reported, and numerous phenotypic expressions have been described[6,8-10]. Proteus syndrome may be difficult to recognize because the manifestations are very diverse and it shares many features common to

Table 1. Scoring system for diagnostic features of proteus syndrome.

Feature	Points*
Macrodactyly and/or hemihypertrophy	5
Skin thickening (plantar and/or palmar cerebriform hyperplasia)	4
Lipomas and subcutaneous tumors	4
Verrucous epidermal nevus	3
Macrocephaly or skull exostoses	2.5
Miscellaneous minor abnormalities	1

* Thirteen or more points are required to establish the diagnosis[2].

other hamartomatous conditions. Samlaska et al[8] classified the clinical features into 2 categories : major clinical findings which were observed in more than half of the reported cases and associated clinical findings which were noted in less than half of the cases. The main clinical features for diagnosis are hemihypertrophy, macrodactyly, subcutaneous tumors, plantar and/or palmar hyperplasia, exostoses, epidermal nevi, and scoliosis. Most of the cases have at least four of these findings. The two most consistent features are macrodactyly and limb overgrowth or hemihypertrophy which may involve part or all of one or more extremities. Darmstadt and Lane[11] developed a scoring system for diagnostic criteria. A score of 13 or more points established the clinical diagnosis of Proteus syndrome (Table 1). This case scored 16.5 points. The only category missing was verrucous epidermal nevus. Miscellaneous minor abnormalities included cryptorchidism and epicanthal folds.

A broad range of clinical features are found in this syndrome. Some manifestations are present at birth[8,9]. Growth disturbances are generally apparent within the first few years of life[9]. In severe cases, abnormalities tend to develop earlier and progress more rapidly[8,12]. Skeletal and soft tissue overgrowth may affect the face, part or the whole limbs and the trunk. Hemihypertrophy may result in severe limb length discrepancy. The overgrowth tends to be accelerated during early childhood[6,8,11]. Macrodactyly, due to overgrowth of phalanges and cartilaginous tissues, may be absent at birth but often progress rapidly in the first few years of life, causing severe cosmetic and functional problems. The disproportionate growth of the affected digits is typically slow in late childhood[9]. Plantar or, less commonly, palmar cerebriform hyperplasia is highly characteristic of the syndrome[9,13-15]. Histological features of tissue taken from the typical cerebriform plantar hypertrophy have demonstrated hyperkeratosis and increased but normal-looking collagen[13]. A number of different cutaneous lesions and subcutaneous masses occur[7]. Subcutaneous tumors of various types, including lipomas, lymphagiomas, hemangiomas, or combinations of these hamartomas may occur in any part of the body, particularly on the thoracic and upper abdominal regions[15]. Pigmented nevi occur at birth or in early life, and may be linear, whorled, and/or verrucous and may be located anywhere on the body[8]. Vascular nevi include port-wine stains, angiomas, and lymphagiomas. Areas of macular hypo- or hyperpigmentation, patchy dermal hypoplasia, and varicosities have been reported[4,13,16]. Non-cutaneous findings include skeletal abnormalities such as skull exostoses, macrocephaly, kyphosis, scoliosis, and spinal canal stenosis. Mental retardation has also been described in Proteus syndrome patients and most of them have associated cranial abnormalities[12,17].

The etiology of Proteus syndrome is unknown. All of the reported cases have been sporadic[15]. Only one reported patient had an abnormal karyotype, a duplication of 1q11→ q 25[18]. Two cases of possible parent-to-child transmission have been reported[19,20]. Based on the sporadic occurrence, the lack of gender predominance, mosaic distribution of lesions, and variable extent of involvement, but never diffuse involvement of the entire body or entire organ system, Happle[21] proposed that a dominant lethal gene survives by mosaicism as a result of an early somatic mutation causes the syndrome. The phenotypic changes may be caused by altered production of local tissue growth factors. Smeets et al[22] reported a patient with regional manifestation of Proteus syndrome, supporting the hypothesis of somatic mosaicism. Rudolph et al[23] found a decreased level of insulin-like growth factor II and insulin-like growth factor-binding protein-3 in fibroblasts obtained from hypertrophied skin in an affected patient. It is speculated that the disproportionate growth of tissue is related to a local imbalance of insulin-like factor binding proteins or to a primary defect in the synthesis of these peptides due to mutations in the growth factor gene.

Proteus syndrome also shares many features common to several other congenital hamartomatous disorders such as Klippel-Trenaunay-Weber syndrome (KTWS), Maffucci syndrome and neurofibromatosis type I (NF-1). Cerebriform hyperplasia of the soles and palms, highly characteristic of Proteus syndrome, is lacking in all other hamartomatous disorders. KTWS is classically composed of port-wine stains, varicose veins, hemihypertrophy, macrodactyly, and epidermal nevi, usually confined to one side of the limb. It lacks subcutaneous tumors, palmar and/or plantar cerebriform hyperplasia and cranial exostoses[8,9]. Maffucci syndrome includes macrodactyly, limb hypertrophy, and asymmetry but can be distinguished from Proteus syndrome by the presence of endochondroma [7]. Proteus syndrome may be distinguished from NF-1 by the absence of multiple café au lait spots, Lisch nodules, freckling, and multiple neurofibromas[4,7].

Management in Proteus syrdrome is primarily by surgical reconstruction[17]. The subcutaneous tumors may become quite large and infiltrate local tissues, making resection difficult. Early consultation with plastic and orthopedic surgeons is crucial. Patients often need radical and disfiguring surgery at a young age. An increased frequency of malignancy is found in many hamartomatous disorders. A mesothelioma and a yolk sac tumor of the testis have been reported in two children with Proteus syndrome[24,25]. It is important to recognize this unusual syndrome early so that treatment and genetic counseling can be properly provided.

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กลุ่มอาการโปรเทียส : รายงานผู้ป่วย 1 ราย

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กลุ่มอาการโปรเทียสเป็นโรคทางกรรมพันธุ์ที่พบได้น้อยมีลักษณะสำคัญประกอบด้วยมือและเท้าที่มีขนาดโตผิดปกติ ขนาดของแขน ขา ที่ไม่เท่ากัน ฝ่าเท้าที่หนาผิดปกติ เนื้องอกใต้ผิวหนังที่เกิดจากความผิดปกติในการเจริญเติบโตของเนื้อเยื่อชนิดต่าง ๆ กระดูกที่งอกผิดปกติและการเจริญเติบโตของกระดูกท่อนยาวที่มากกว่าปกติ ได้รายงานผู้ป่วย 1 ราย เป็นผู้ป่วยเด็กชายไทยอายุ 1 วัน ซึ่งมีลักษณะตัวโต มีใบหน้าซีกซ้ายใหญ่กว่าซีกขวา ขาข้างซ้ายใหญ่กว่าขาข้างขวาและมีนิ้วเท้าขนาดใหญ่ หนังบริเวณฝ่าเท้าหนา เนื้องอกใต้ผิวหนังขนาดใหญ่บริเวณหน้าอกด้านซ้าย และปานแดงขนาดใหญ่บริเวณหน้าอกด้านขวา รายงานนี้ได้ทบทวนและนำเสนออาการแสดงทางคลินิก เกณฑ์การวินิจฉัยโรค การวินิจฉัยแยกโรค และการรักษา

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