

Proteus Syndrome: A Natural Clinical Course of Proteus Syndrome

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A 16-year-old Korean male patient presented with macrodactyly, hemihypertrophy of the face and extremities, plantar cerebriform hyperplasia, a subcutaneous mass of the left chest, macrocephaly and verrucous epidermal nevi. These findings are consistent with Proteus Syndrome. The clinical features, etiology, management, natural course and differential diagnosis of this case are discussed.

Key Words: Macrodactyly, hemihypertrophy, proteus syndrome

INTRODUCTION

Proteus Syndrome is a rare disorder first described in 1983 by Wiedemann et al.¹ Since then, approximately 188 articles have been reported from various countries. The polymorphism of the disease, emphasized by its name, has become increasingly evident. Two cases of this disease have been reported among ethnic Koreans. The first case was a 9 year-old child reported in 1988.² The second case was diagnosed in 1986 and first reported in Germany in 1997. However, the publication was only a cross sectional report. Furthermore, the case reports from Korea were only reported in Korean.

We encountered the second case mentioned above in 1999. This report is a detailed follow-up observation of the anatomical changes associated with the disease in this patient from birth to age

16 years and a review of the relevant literature. We plan to continue following this case and will make future reports. Because of the lack of understanding of the clinical features and course of this syndrome, it is our hope that this report will be of assistance in diagnosing and managing future cases and in understanding the natural course of this disease entity. In addition, by writing this report in English, we would like to share our information with a broader audience and obtain advice on the available therapeutic options.

CASE REPORT

A 16-year-old Korean male presented to us. He had experienced swelling in his left leg from October 1998 to February 1999 that had not totally resolved. The patient had initially experienced pain in the left leg and was seen at the Veteran's Rehabilitation Center. There, his condition was thought to be caused by chronically walking on his heel. When edema continued for several months, his mother voiced concern over the potential for permanent damage to his leg. The swelling gradually improved, with residual hyperpigmentation. At present the patient's main problem is a recurrent hyperkeratosis of the amputated stumps and macropodia, which produces problems in fitting shoes. The patient and his mother requested that he have corrective surgery, and possibly a prosthesis that would enable him to wear normal shoes. In all other respects, the patient is in good health.

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Infancy

A more detailed description reveals an infant born uneventfully after a 43-week gestation. He was the first child of a healthy 24-year-old mother and 29-year-old father. His parents and two siblings have not had any cutaneous abnormalities, and up until the present, have been free of any apparent diseases. At birth, he weighted 2950g (25 percentile) without any gross abnormalities. At the age of 6 months, his mother noticed abnormal changes in his limbs, such as the hypertrophy and macrodactyly of the child's left hand and left lower extremities with hyperpigmented nevi on the left forearm. However, the patient's growth and development until this time were considered normal.

Early childhood

At the age of 2 1/2 years (1986), he was referred to the Child Endocrinology Clinic at Seoul National University Hospital, where the endocrinologist diagnosed him as having no abnormalities. Later in his early childhood, it was suggested that he might have neurofibromatosis or some other unknown dermatologic disease. Later in 1986, a physical examination showed deformities and overgrowth of the left upper extremity, along with port-wine stains on the left side of his neck, axilla, back, hand, and posterior-medial part of both thighs. The child was followed without a definitive diagnosis until 1987, when he was diagnosed in Germany as having Proteus Syndrome. At that time (3 1/4 years of age), an enlargement of the left hand and foot had become obvious, and four sequential surgical procedures were performed in Germany. The first was a corrective epiphysal osteotomy on his left knee. Consecutive corrective surgeries were undertaken on the same knee in July 1989, July 1990, and July 1992.

The leg-length discrepancy noted in infancy became more pronounced as he grew older. At 4 1/2 years, the length of his left leg was 5.5cm greater than his right, and the range of motion of his left knee was 90-70-0 (flexion/extension). At the age of 5 1/2 years, he had an osteotomy of the left femur and arthrolisis of the left knee, which shortened his left leg by 4cm. Eight months

later the length difference between both legs was 3.5 cm, with his left leg having grown 2 cm after the operation.

Late childhood

At the age of 8 3/4 years, an extension osteotomy was performed on the distal femur of the left knee for a knee and hip contracture on the left extremity that caused a 10-degree knee flexion. After this, a hypertrophic overgrowth was found on the left knee joint, and the knee contracture became 40 degrees. Because of this, another corrective osteotomy and plication of the joint capsule was done on the left knee.

At the age of 12 (1995), the child was re-evaluated at the Veterans Hospital in Korea. His height was 157 cm and his weight was 36 kg. His alkaline phosphatase was somewhat elevated at 363 IU/L (single measurement), while his IGF-II (insulin-like growth factor-II) level was somewhat decreased at 95.7 mg/ml.

Recent history

Our first encounter with this patient was on August 17, 1999 when he was 16 years of age. At that time, he had a height of 169 cm (50th percentile, average: 170 cm) and weight of 52 kg (25 - 50th percentile, average: 62 kg). His vital signs were: BP 110/60 mmHg, PR 78/min, RR 18/min, BT 96.7° F. His health was generally good and he appeared to be of normal intelligence.

Brownish verrucous lesions and whirled brownish patches were distributed on the middle of his forehead, the left side of his neck, forearm, back, hand, and both axilla. The lesions on the arm were linear. Brownish and verrucous lesions were located on the left side of the abdomen. There was no edema, cyanosis, stasis or ulcerations on the upper extremities. However, the right leg had severe superficial varicosities (Fig. 1). It had a port-wine stained red macule involving the medial half of the sole and big toe (Fig. 2). There was no abnormal skin pigmentation on the rest of the body. The hair was symmetrically distributed except on the left side of the back and the left extremity where growth was more pronounced. The axilla showed no hair growth. The genital and

pubic hair growth patterns were normal at Tanner stages V and IV, respectively. There was no clubbing of the digits, but there was a pitting lesion on the nail of the left 4th digit (Fig. 1). A lymph node approximately 0.3 cm in diameter was palpable along the anterior neck.

An eye examination showed no abnormal findings. The patient's vision by Snellen scale was 20/200 right, 20/50 left (uncorrected); 20/40 right, 20/35 left (corrected). His ear, nose and throat examination results were within normal limits.

There was a 3 × 4 cm soft, non-tender and non-moveable mass within the right axilla. Two palpable nodules were located during the breast exam. One nodule located under the left nipple, was soft, non-tender, and freely movable. The other nodule was located between T5 and T7 of the left anterior axillary line.

The chest muscles and respiratory efforts were symmetric, with no use of accessory muscles. On percussion, the lungs were resonant throughout, with 4 cm of bilateral excursion. His breath sounds were clear to auscultation bilaterally. Examination of the cardiovascular system and abdomen showed normal findings. There were no carotid, renal, or abdominal bruits.

In the upper extremities, his left arm, 72 cm in length, showed a cubitus varus and was 3 cm longer than the right arm. The index and middle fingers of his left hand showed macrodactyly with ulnar deviation. On the right hand, there was ulnar deviation of the index, middle and 4th digit DIP joints. There was variation in the width of the right and the left hand from the 2nd to 5th MCP joints. Impaired overall flexion was also noted at the DIP and PIP joints, with limited motion at the MCP joints of his the left hand (Fig. 1).

There was cerebriform hyperplasia on the left sole. A soft tumor was also noted on the right big toe. The left foot was larger than the right foot (Fig. 2). There was no pedal edema, swelling, or tenderness on the lower extremities. The Homan's sign was negative. The left leg showed a Pes valgum and Genu recurvatum. The angulation of the Genu recurvatum was 35 degrees (Fig. 3).

There were no abnormalities or masses on the penis, scrotum, testes, or epididymis. A rectal exam revealed no abnormal findings. There was no evidence of any masses in the abdomen and no

splenomegaly was shown in the abdominal CT.

On neurological examination, the cranial nerves I-XII were grossly intact, and the cerebellar function tests were normal. Muscle strength was adequate, with a full range of active and passive motion except for the left hand and knee. The deep tendon reflexes were normal except for the left knee joint.

Laboratory tests showed the following: ESR 3, Total bilirubin 0.3 g/dL, ALP 3.0 IU/L, Albumin 4.5 g/dL Urine testing showed protein 3+, but a follow up study space 3 weeks later showed no protein in the urine, pH of 5.0, Blood (-), SG 1.039, Urobilinogen 0.2. Stool Guaiac test (performed in triplicate) was negative. H. pylori serologic tests were positive for both IgM and IgG. A chromosomal study showed normal findings.

We reviewed the histopathology biopsy materials from Germany. The microscopic examination showed that the articular cartilage was expanded by a hyperplastic hyaline and fibrous cartilage, with focal myxoid changes (Fig. 4A). In addition, the fibrous cartilage showed a multinodular growth pattern at the periphery of the articular cartilage with a pushing margin (Fig. 4B), and the hyaline cartilage showed a disordered chondrocyte proliferation with mild atypia and binuclei (Fig. 4C). The cancellous bone was osteoporotic with markedly disrupted bony trabeculae (Fig. 4D).

DISCUSSION

Proteus Syndrome is a rare disorder manifesting itself in a variety of ways. In the initial description of Proteus Syndrome, Wiedemann et al. proposed the following diagnostic criteria: 1) gigantism of the hands and/or feet, 2) pigmented nevi, 3) hemihypertrophy, 4) subcutaneous tumors, 5) skull abnormalities, 6) early accelerated growth, and 7) visceral anomalies.^{1,3} Considered individually, none of these major criteria are specific to or pathognomonic for Proteus Syndrome. With this in mind, Hotamisligil designed a scoring system in 1990 to assist clinicians in making a definitive diagnosis.⁴ This was modified in 1994 by Darmstadt and Lane (Table 1).⁵ According to this scale, which assigns relative point values to the first five criteria above, the patient in this



Fig. 1. Lesions on the arm were linear. Brownish and verrucous lesions were located on the left side of the abdomen. There was no edema, cyanosis, stasis or ulcerations on upper extremities. The patient's lower extremities showed pink, with marked superficial varicosities in the right leg. There was no clubbing of the digits. On the right hand, there was ulnar deviation of the index, middle and 4th digit DIP joints. There was variation in the width of the right and the left hand from the 2nd to 5th MCP joints. Impaired overall flexion was also noted at the DIP and PIP joints, with limited motion at the MCP joints of his left hand. The index and middle fingers of his left hand were abnormally enlarged with prominent ulnar deviation. His left arm showed cubitus varus and was longer than the right arm.

Table 1. Scoring System for the Diagnosis of Proteus Syndrome

Feature	Score
Macroductyly and/or hemihypertrophy	5
Plantar and/or palmar cerebriform hyperplasia	4
Lipomas and subcutaneous tumors	4
Verrucous epidermal naevus	3
Macrocephaly or skull exostoses	2.5
Micellaneous minor abnormalities	1

A score of 13 or more is required to establish a diagnosis.

report had a "definitive" diagnosis of Proteus Syndrome. Abnormalities of six categories were present in this patient. With a score of 13 or more points required to establish a definitive diagnosis, our patient scored 19.5 points, clearly fitting the diagnosis of Proteus Syndrome. The patient's



Fig 2. Hemihypertrophy was noted on the 1st and the 2nd toe with hallux valgus of the left great toe. There were cerebriform hyperplasia on the left sole. A soft tumor was also noted on the right great toe. The left foot was bigger than the right foot.



Fig. 3. In the lower extremities, left leg showed Pes valgum and Genu recurvatum. The angulation of the Genu recurvatum was 35 degree. The right knee also showed hyperplastic overgrowth.

low-set ears were also included in this scoring system as a miscellaneous minor abnormality.

Because of the sporadic appearance and normal chromosomal features of patients affected with this syndrome, the etiology and inheritance of Proteus Syndrome are uncertain. Recently, Bieseker et al. reviewed the recommendations for the diagnostic criteria, differential diagnosis, and

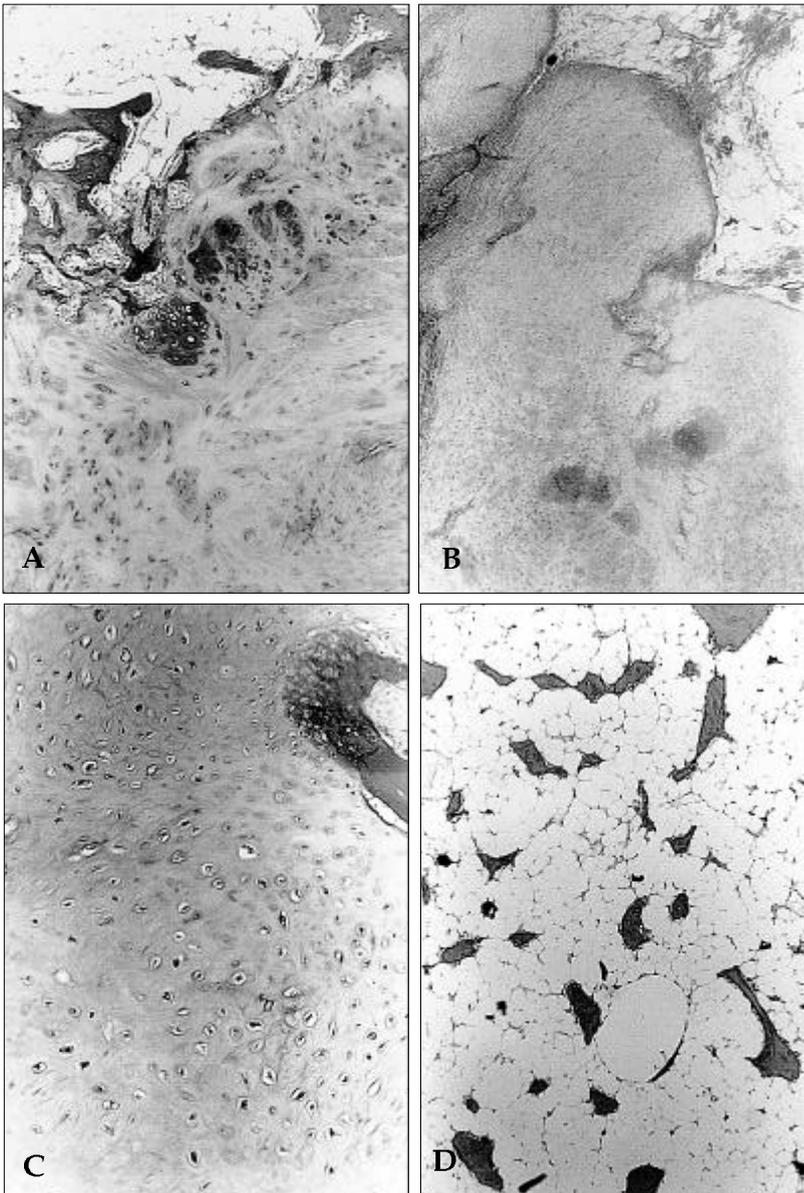


Fig. 4. The microscopic examination showed that the articular cartilage was expanded by a hyperplastic hyaline and fibrous cartilage, with focal myxoid changes (A, $\times 40$), that the fibrous cartilage showed multinodular growth pattern at the periphery of the articular cartilage with pushing margin, (B, $\times 20$) that the hyaline cartilage had a disordered chondrocyte proliferation with mild atypia and binuclei, (C, $\times 100$) and that the cancellous bone was osteoporotic with markedly disrupted bony trabeculae (D, $\times 40$).

guidelines for evaluating patients suspected of having Proteus Syndrome, that were developed in 1998 at a workshop at the National Institutes of Health.⁶ Mosaic distributions were suggested as mandatory to meet the diagnostic criteria. Connective tissue nevi, common manifestations in Proteus Syndrome, were considered almost pathognomonic for the syndrome, although they are not present in every case. Other combinations of manifestations (e.g., epidermal nevus, disproportionate overgrowth, specific tumors) were suggested to meet the diagnostic criteria.

In all but two reported cases, the parents of

affected children were nonconsanguineous. With one possible exception, routine karyotyping studies have shown a normal chromosomal structure.⁷ A dominant somatic mutation, lethal in the non-mosaic state, has been suggested to be the underlying cause of Proteus Syndrome.⁸ Mutation-altered growth factors, the receptor response, or a PTEN mutation may explain the polymorphic aspects of the disorder.⁹⁻¹¹ A duplication of 1q11 \rightarrow q25 was found in one child with features of Proteus Syndrome.⁷ This suggests the possibility that this phenotype results from the interruption of a coding sequence or from an abnormal dosage

due to gene duplication.⁷ Because of the variable asymmetric features, it has been proposed that a dominant lethal gene survives by mosaicism as a result of an early somatic mutation.^{8,12} Our patient also showed a normal 46XY karyotype with no evidence of any chromosomal abnormalities. One group found decreased levels of IGF-II and the insulin-like growth factor binding protein-3 in the fibroblasts obtained from the hypertrophied skin in an affected patient. Affinity cross-linking experiments showed the fibroblasts in the affected tissue exhibited a disturbed production of the insulin-like growth factor.¹⁰ Our patient showed a decreased level of IGF-II in 1997.

Functional abilities and longevity vary with the severity of the limb and brain anomalies. Reported brain anomalies include hypocephalus, craniosynostosis, hemimegalencephaly, and an absent corpus callosum.¹³⁻¹⁵ Skull abnormalities include exostoses, most commonly in the frontotemporal or parietooccipital regions, macrocephaly, and a skull asymmetry due to hemihypertrophy. Scoliosis or kyphoscoliosis occurs in approximately half of all patients. Our patient had no macrocephaly, but multiple thickening and skull exostosis were found on the left frontoparietal and right occipital area. Prominent sinus was found in the left forehead. A brain MRI showed no gross abnormalities in the brain parenchyma, cerebellum, brain stem and the ventricular system (Fig. 5). Furthermore, there was no definitive scoliosis or kyphoscoliosis. Although the patient has a problematic gait, it was attributed to the bony deformity rather than cerebellar or other neurological dysfunctions. Approximately two-thirds of patients with Proteus Syndrome have normal intelligence and achieve normal developmental milestones.⁴ However, our patient's grades at school were extremely poor, as his rank was 58 out of 59 in his class. Of those who are mentally retarded, 88% have associated cranial abnormalities.⁴ Our patient did not have cranial nerve anomalies, facial asymmetry, eye abnormalities, mental retardation, or seizures.

There are seven salient features of Proteus Syndrome, each of which develops in a majority of patients. The two most consistent features are a macrodactyly of any combination of the digits in the hands and feet, and limb overgrowth or

hemihypertrophy, which may involve part or all of one or more extremities. Macrodactyly or asymmetric growth are found in 98% of patients.⁴ Macrodactyly is primarily due to the overgrowth of phalanges and cartilaginous masses, but it may also involve the overgrowth of subcutaneous tissues.¹⁶ Growth disturbances are generally apparent within the first few years of life, and in severe cases, abnormalities tend to develop earlier and progress more rapidly.^{4,17} The disparity between normal, overgrown limbs and digits become relatively less noticeable in late childhood and adolescence. Tissue overgrowth of Proteus Syndrome appears to plateau after adolescence (15 - 17 years of age) when the growth plate activity slows down.⁹

Our patient showed a generalized left-sided hypertrophy and macrodactyly on the left 1st, 2nd and 3rd fingers and 1st and 2nd toes, along with unequal growth between the upper and lower extremities, hypertrophy of the left knee and an angulation deformity of the left knee (Fig. 1, 3, 6, 7). The patient had a corrective osteotomy 5 times in early childhood. Similar findings were observed on the right leg, but were much less pronounced. This patient will most likely need additional corrective surgery after his growth plate closes.

Subcutaneous tumors of various types, including lipoma, lymphangioma, hemangioma, or various combinations of these hamartomas occur most commonly in the thoracic, epigastric, and



Fig. 5. Brain MRI: Multiple thickening and skull exostosis of the left frontal and the right occipital bone. Prominent left frontal sinus. No gross abnormalities of the brain parenchyma. Normal cerebellum and brain stem. Normal ventricular system.



Fig. 6. Knee (external AP): Osteolytic bone tumor with large bulging contour involving left epiphysis, distal femur, and proximal tibia and fibula. Multilinear or amorphous calcification noted inside the tumor. Bulging osteolytic bone tumor on the superior portion of the right patella. Multiple irregular osseous bodies in knee joints and politeal area, suggesting loose bodies. Radiologic imp: Multiple bulging contour osteolytic bone tumor in both knees, most likely enchondromatosis with involving of both epiphysis and metaphysis.



Fig. 7. Left foot AP: Large bulging osteolytic bone tumor observed in the epiphysis of the distal tibia, fibula, tarsal bone, metatarsal bone and phalangeal bone, involved in the epiphysis and metaphysis. Also, a severely destructive bone change was observed on the above area and hypertrophic skin on the plantar area. This finding compatible with the enchondromatosis.

gluteal regions.⁵ Verrucous epidermal nevi are present at birth or soon after birth.⁴ They are most commonly linear but may be whorled, and can be located anywhere on the body.^{1,5} Other subcutaneous findings include areas of decreased subcutaneous fat, a superficial venous prominence, varicosities, and rarely a cafe au lait macule.^{4,17} Plantar and, less commonly, palmar cerebriform hyperplasia are highly characteristic of Proteus Syndrome; some authors believe that this finding is pathognomonic.¹⁸ Our patient presented with dark brown pigmented nevi on the left neck, shoulder, upper arm and forearm, cerebriform hyperplasia of the left foot, and subcutaneous lipomas on the left upper and lower extremities, left chest, abdomen and back (Fig. 1 and 2).

It has been reported that Proteus Syndrome shares features with several other congenital hamartous disorders. However, with the time required to express the phenotype, the diagnosis may not be certain for months or even years. The well-defined criteria for diagnosing neurofibromatosis, including the presence of cafe-au-lait macules, neurofibromas, axillary freckling, Lisch nodules, optic glioma, and autosomal dominant

inheritance, make its distinction from Proteus Syndrome clear.⁵ Bannayan-Zonana syndrome includes macrodactyly, subcutaneous lipomatosis, and megalencephaly. However, it lacks the asymmetric growth, skull exostoses, and epidermal nevi.¹⁹ Mafucci syndrome includes macrodactyly, limb hypertrophy, and asymmetry, but can be distinguished by the presence of enchondromata and retardation of long bone growth.¹⁹ Klippel-Trenaunay-Weber syndrome lacks exostoses, and major arteriovenous malformations are characteristic of the Parke-Weber variant of Klippel-Trenaunay-Weber syndrome.^{4,14,19} The vascular changes of Proteus Syndrome are limited to the dilatation of the superficial veins at the sites of hypertrophy and superficial hemangioma.⁴

Beyond diagnosis, little information is currently available on the underlying disease and its medical management, with further research remaining to be done.

Surgical reconstruction is considered to be the primary mode of rehabilitating children with Proteus Syndrome. However, it is not always the best option provided the abnormalities do not interfere with normal activities. The sites of involvement requiring particular attention and consolidation for early reconstructive surgery are the

large subcutaneous masses in and around the neck, which may compromise the airway, thoracic paraspinal masses, digital gigantism involving the hands and feet, and long bone length discrepancies, especially of the lower limbs, that may interfere with ambulation.¹⁹ Surgical intervention and treatment is difficult due to frequency of complications and recurrence. Worldwide, there is insufficient clinical experience with this disease entity. Consequently, there is little information regarding the effect of frequent surgical intervention. Fortunately, the progression of Proteus Syndrome appears to stop at 15 - 17 years of age.⁹ Therefore, surgical intervention may be more effective than and it may be advantageous to wait before performing the repeated definitive surgeries.²⁰

Recent advances in genetics may provide new treatment modalities. Because Proteus Syndrome is sporadic, it is hypothesized to be caused by somatic mutation. Efforts are under way to characterize the difference in gene expression or genomic abnormalities in paired affected and unaffected tissues from Proteus patients. Characterization of the molecular defects should not only allow accurate diagnosis of the condition, but may also provide hope for an effective treatment of the underlying pathophysiology.²¹ Moreover, with the completion of the Human Genome Project, a more comprehensive understanding of the pathogenesis of this disease could lead to new therapeutic options such as gene therapy.

By publishing this report, we hope to obtain knowledge of other cases throughout the world so we can offer better therapeutic options for this patient. In addition, we hope this report may result in further advice and discussion regarding surgical and/or gene therapy for this patient. In the future, our team plans to continue to follow this patient on a 5-year basis in an attempt to map the natural clinical course of the disease and describe its management.

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