Proteus syndrome of the foot: A case report and literature review

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Abstract. Proteus syndrome (PS) is an extremely rare and sporadic disorder characterized by asymmetric and/or disproportionate overgrowth of limbs, hamartomas, and vascular malformations. The onset of overgrowth usually involves the skin, bone, fat, and other connective tissues in a patchy or mosaic pattern. Partial gigantism of the affected limb or digit is a pathognomonic sign of PS. Thus far, only a few cases of PS have been recorded in the literature. In the present report, a case of PS in a 35-year old woman with classic cerebriform plantar hyperplasia and macrodactyly of the left foot was documented. The clinical and molecular characteristics and differential diagnosis of PS are also discussed in this report.

Introduction

Proteus syndrome (PS) is a sporadic hamartomatous syndrome that manifests as asymmetric overgrowth of body parts, hyperplasia of connective tissues, hyperostosis, hemangiomas, lipomas, tumors, disordered adipose tissue, nervous system complications, and vessel malformations (1,2). This syndrome was first described by Cohen and Hayden in 1979 (3), and named 'Proteus syndrome' by Wiedeman in 1983 (4). It causes overgrowth of multiple tissues in a patchy or mosaic pattern, and commonly affects tissues that include but are not limited to the skin, connective tissue, bones, nervous system, and eyes, which determine disease severity in different patients (2,5). The onset of PS typically occurs in childhood, with more complex manifestations developing over time (6). Its approximate incidence is one per 1 million (7). Clinical manifestations perceived to be diacritic include macrodactyly deformities, unilateral hypertrophy, palmar or plantar cerebriform hyperplasia, subcutaneous tumors, verrucous nevus, exostosis, and vessel hamartomas (8,9). At present, somatic mosaicism is the widely accepted hypothesis for the etiology of PS (7); however, this disorder has not been fully understood. In the present report, a rare case of PS that presented with massive excrescence and cerebriform plantar hyperplasia of the left foot was documented. Furthermore, given that PS overgrowth typically manifests between the ages of 6 and 18 months, this case is unusual owing to the solitary cutaneous finding and delayed presentation in the fourth decade of life. Current available literature on the syndrome was also discussed.

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Materials and methods

Sections of 4 μm thickness were made from formalin-fixed (10% neutral-buffered formalin at 4˚C for 24 h) paraffin-embedded block. The sections were then rehydrated by xylene and a descending ethanol gradient, following which they were stained with Verhoeff-van Gieson method under the standard protocol for confirmation of diagnosis (10). The stained slides were observed under a light microscope. Two independent observers evaluated all the slides to reduce subjective bias. The elastic fibers were analyzed at magnifications, x10 and x40 for density, morphology, pattern of grouping. Statistical analysis was conducted using χ^2 test.

Case report

A 35-year-old woman visited First Affiliated Hospital of Kunming Medical University (Kunming, China) for treatment of progressive postnatal overgrowth involving her left foot. The patient observed swellings and excrescences on the fourth and fifth toes of the left foot for the past 10 years, but did not exhibit any other subjective symptoms. Despite undergoing surgical excision at a local hospital at Kaiyuan, Yunnan, the patient experienced recurrence with enlarged hyperplasia and an expanded rash. She terminated further treatments. However, the affected tissue continued to grow over the years, seriously affecting the daily life of the patient. Thus, the patient was admitted to our hospital in July 2018. Cutaneous examination revealed the presence of a massive soft tissue hyperplasia in the fourth and fifth toes and classic cerebriform plantar hyperplasia of the foot (Fig. 1A). There was no similar overgrowth observed in any other part of the body, and no other member of the patient's family exhibited similar features.

Physical examination showed apparent discrepancy in the thickness of both lower limbs, varicosity, joint deformity, or

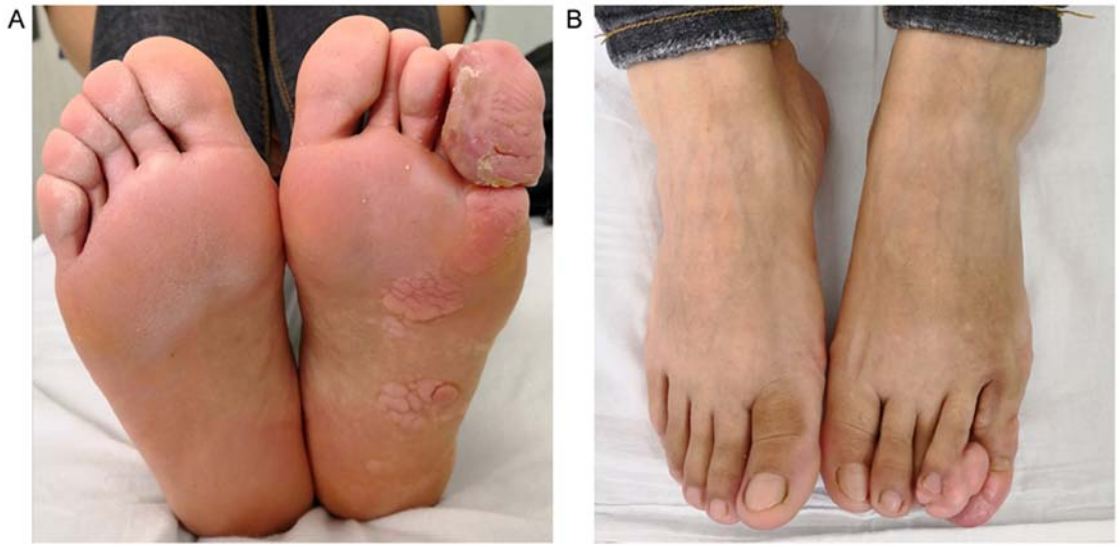

Figure 1. (A) Macrodactyly and cerebriform plantar hyperplasia on the left foot. (B) Enlarged fourth and fifth toes with irregular bulges.

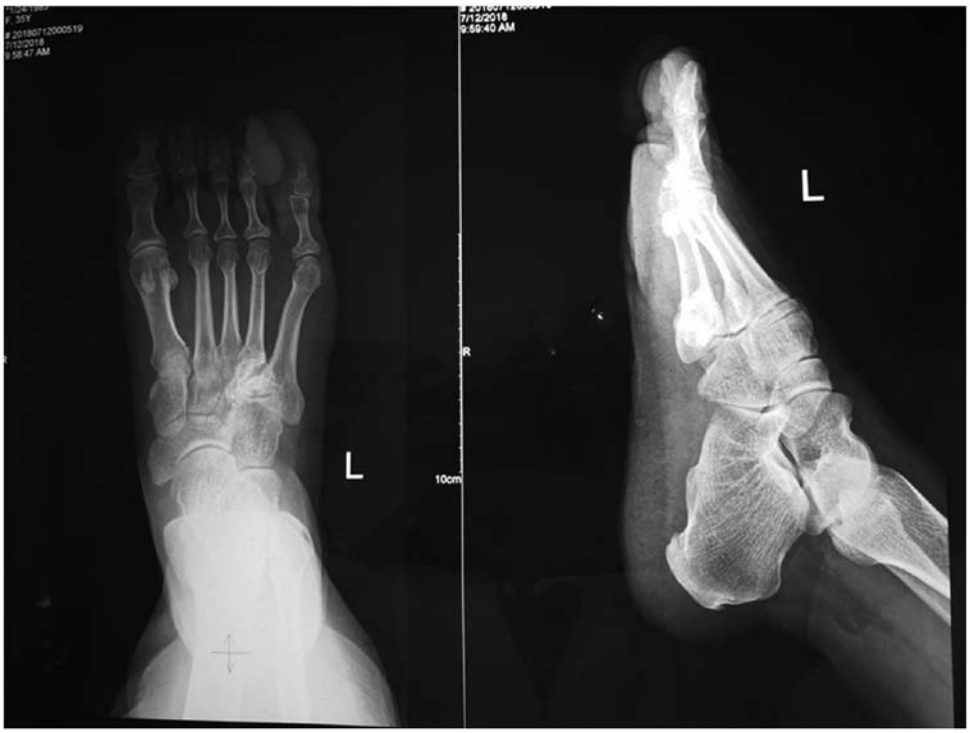

Figure 2. Radiography of the left foot of the patient. This radiograph demonstrates soft tissue masses around the affected phalanxes and irregular bone structure of the fourth phalanx.

scoliosis. Cerebriform hyperplastic tissues of different size were observed in the planta. The epidermis of the hyperplastic area was significantly thickened owing to keratinization; however, there was no evidence of ulceration (Fig. 1B). There were no port-wine stains, hemangiomas, or purpura.

Radiography of the affected lower limb showed soft tissue masses around the phalanxes of the fourth and fifth toes, and irregular bone structure of the phalanxes (Fig. 2). Histopathologic examination of the hyperplastic tissues revealed normal structure of the epidermis. However, collagen in the dermis was thickened and disorderly arranged. In addition, elastic fibers were also decreased in the affected dermis (Fig. 3). Based on the clinical features and results from the histopathological and radiological evaluation, the patient was diagnosed with PS.

Discussion

PS affects more male than female patients with a ratio of approximately 2:1 (11). However, its prevalence is evenly

Table I. All recent published research reports regarding Proteus syndrome (PS) cases with foot involvement.

Title of article (refs.)	Year
Reassessment of the Proteus syndrome literature: Application of diagnostic criteria to published cases (11)	2004
A mosaic activating mutation in AKT1 associated with the Proteus syndrome (19)	2011
Proteus syndrome: Three case reports with a review of the literature (28)	2012
Proteus syndrome: Clinical profile of six patients and review of literature (29)	2013
Thoracolumbar scoliosis in a patient with Proteus syndrome: A case report and literature review (30)	2015
Island nail flap in the treatment of foot macrodactyly of the first ray in children: report of two cases (31)	2015
Recurrent cerebriform connective tissue nevus on the foot of a patient with Proteus syndrome (32)	2016
Proteus syndrome: A case report and review of the literature (14)	2017
Proteus syndrome (33)	2017
Case report: 'Incognito' Proteus syndrome (34)	2018

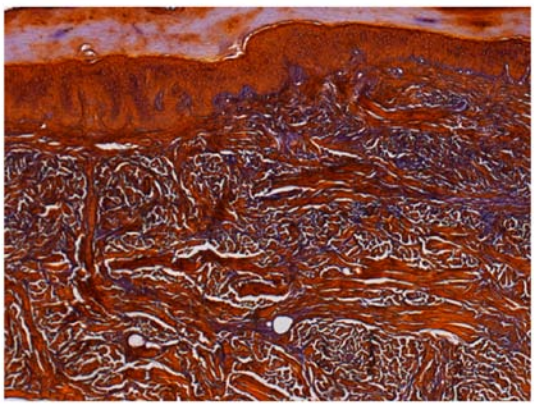

Figure 3. Biopsy of the affected tissue. Thickened collagen and decreased elastic fibers in the affected tissue were observed. Magnification, x200.

distributed among ethnic groups (12). Recently reported PS cases associated with the foot is summarized in Table I. This disease is hardly noticeable at birth; however, its diagnosis is challenging in the early stage owing to the involvement of multiple tissues (13). Moreover, the vast clinical variability in PS probably results in misdiagnosis (14).

Macrodactyly is characterized by hypertrophy of the bone with hamartomatous overgrowth of several fibro-adipose structures without any other associated skin lesions and systemic involvement. Bannayan-Zonana syndrome associates macrocephaly, polyposis of the colon and subcutaneous lipomas (15). Maffucci syndrome combines enchondromatosis and haemangioma (16). Ollier disease shows enchondromatosis with possible malignant transformation and cerebral neoplasms (17). PS exhibits more features of reticular connective tissue naevi, which are not manifested in Klippel-Trenaunay-Weber syndrome (18).

Lindhurst *et al* (19), found that a somatic activating mutation (c. G49A, p. E17K) in the oncogene *AKT1* was associated with the severity of PS. Subsequently, Valera *et al* (6) proposed that a genetic test for the *AKT1* mutation in affected and adjacent non-affected tissues could be a more accurate approach to confirm the diagnosis. However, a few cases did not show any association between the *AKT1* mutation and PS, including three of the 29 patients with PS reported by Ou *et al* (14) and Lindhurst *et al* (19). It was speculated that somatic mutations in another gene-phosphatase and tensin homolog (*PTEN*)-causing dysfunction of the PI3K-AKT pathway may be potential causes of PS (20,21). However, this hypothesis was rejected based on recently published evidence (22,23), wherein numerous affected individuals with *PTEN* mutations and clinical features of 'Proteus-like syndrome' were eventually diagnosed with SOLAMEN (segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus) or Cowden syndromes. In 1987, Happle suggested a pathogenetic theory stating that PS is caused by somatic alteration in a gene resulting in mosaic effects that could be lethal if the mutation presented in a non-mosaic pattern (24); however, no PS-associated gene has been identified thus far. Comparison of the present case with another one published by Ou *et al* (14) revealed a considerable difference in severity. According to Happle's theory, an earlier postzygotic alteration in the patient with PS would result in more severe manifestations, as the earlier mutation would have affected a larger number of cell lineages. Thus, further investigation is required to identify the specific genes associated with the development of PS.

At present, the diagnosis of PS is mainly based on clinical manifestations and imaging techniques (25). In 2004, Turner *et al* revised the diagnostic criteria for the syndrome (11), which comprise three general and three specific criteria categories (Table II). For a confirmed diagnosis, the patient should fulfill all the general criteria, namely mosaic distribution of the phenotype, sporadic emergence, and progressive course. Subsequently, an additional single sign from category A, two signs from category B, or three signs from category C are sufficient to establish the diagnosis of PS (26). In the present case, the diagnosis was based on the patient fulfilling all three general criteria and three of the specific criteria, namely cerebriform connective tissue nevus (category A), asymmetric and disproportionate overgrowth of the digits (category B), and dysregulated adipose tissue (category C).

The treatment of PS is challenging owing to its varied clinical features. The patients ought to be periodically followed up for the development of complications (27). Surgical treatment is generally applied for the removal of symptomatic lesions. Given the increasing operative difficulty

Table II. Diagnostic criteria of Proteus syndrome (11).

General criteria (diagnosis includes all of the following):
• Mosaic distribution of lesions • Sporadic occurrence • Progressive course
Specific criteria categories (Either Category A or 2 from Category B or 3 from category C)
A. 1. Cerebriform connective tissue nevus (skin lesions characterized by deep grooves and gyrations as seen on the surface of the brain).
B. 1. Linear epidermal nevus Asymmetric, disproportionate overgrowth (asymmetric, disproportionate overgrowth should be carefully distinguished from asymmetric, proportionate overgrowth) ≥1 of: a. Limbs: Arms/legs/hands/feet/digits b. Skull (hyperostosis) c. External auditory meatus (hyperostosis) d. Vertebra (megaspondylodysplasia) e. Viscera: Spleen and/or thymus Specific tumors before 2nd decade One of the following: a. Ovarian cystadenoma b. Paratid monomorphic adenoma
C. 1. Dysregulated adipose tissue Either one: a. Lipomas b. Regional absence of fat Vascular malformations One or more: a. Capillary malformation b. Venous malformation c. Lymphatic malformation Lung cysts Facial phenotype (the criteria have been found, to date, only in PS patients who have mental deficiency, and in some cases, seizures and/or brain malformations). All: a. Dolichocephaly b. Long face c. Down slanting palpebral fissures and/or minor ptosis d. Low nasal bridge e. Wide or anteverted nares f. Open mouth at rest

and rate of complications over time, early surgical interventions are vital to reduce extra malformations, physical defects, or loss of movement (6). In addition, it is necessary to monitor the patients for potential tumor development. Moreover, the disfiguring impairments characteristic of PS can place enormous psychological burden on patients and their families; thus, psychological counseling is of great importance (28).

Prognosis is closely related to the severity of complications. Approximately 20% of patients with PS expire prematurely, commonly due to venous thromboembolism or pulmonary embolism, pneumonia, or surgical complications (1,28).

In summary, PS is a very rare, highly variable, and progressive tissue overgrowth disorder. The exact pathogenesis and etiology of this disease remain incompletely understood. Considering the complications and early mortality observed in patients, we emphasize the significance of early diagnosis of PS and the need for interventions through a multi-disciplinary approach must be emphasized.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

Authors' contributions

MH made significant contributions to data analysis and literature search, and was a major contributor in writing the manuscript. WZ made substantial contributions to conception and design, and revised the manuscript critically for important intellectual content. Each author agreed to be accountable for all aspects of the work related to the accuracy or integrity of any part of the work, and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of The First Affiliated Hospital of Kunming Medical University (Kunming, China). Informed consent was obtained from the patient in the present study.

Patient consent for publication

Patient consent was obtained from the patient for publication of this report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Biesecker LG, Happle R, Mulliken JB, Weksberg R, Graham JM Jr, Viljoen DL and Cohen MM Jr: Proteus syndrome: Diagnostic criteria, differential diagnosis, and patient evaluation. Am J Med Genet 84: 389-395, 1999.
2. Cohen MM Jr: Proteus syndrome: An update. Am J Med Genet C Semin Med Genet 137C: 38-52, 2005.
3. Cohen MM Jr and Hayden PW: A newly recognized hamartomatous syndrome. Birth Defects Orig Artic Ser 15: 291-296, 1979.
4. Wiedemann HR, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ and Schirg E: The proteus syndrome. Partial gigantism of the hands and/or feet, nevi, hemihypertrophy, subcutaneous tumors, macrocephaly or other skull anomalies and possible accelerated growth and visceral affections. Eur J Pediatr 140: 5-12, 1983.
5. Furquim I, Honjo R, Bae R, Andrade W, Santos M, Tannuri U and Kim C: Proteus syndrome: Report of a case with recurrent abdominal lipomatosis. J Pediatr Surg 44: E1-E3, 2009.
6. Valéra MC, Vaysse F, Bieth E, Longy M, Cances C and Bailleul-Forestier I: Proteus syndrome: Report of a case with AKT1 mutation in a dental cyst. Eur J Med Genet 58: 300-304, 2015.
7. Biesecker L: The challenges of proteus syndrome: Diagnosis and management. Eur J Hum Genet 14: 1151-1157, 2006.
8. Cavero JA, Castro EG and Junco L: Proteus syndrome. Int J Dermatol 39: 707-709, 2000.
9. Yasuda H, Yamamoto O, Hirokawa H, Asahi M, Kashimura M and Sakai A: Proteus syndrome. Dermatology 203: 180-184, 2001.
10. Dahal S, Swaminathan G, Carney S, Broekelmann T, Mecham R and Ramamurthi A: Pro-elastogenic effects of mesenchymal stem cell derived smooth muscle cells in a 3D collagenous milieu. Acta Biomater 105: 180-190, 2020.
11. Turner JT, Cohen MM Jr and Biesecker LG: Reassessment of the proteus syndrome literature: Application of diagnostic criteria to published cases. Am J Med Genet A 130A: 111-122, 2004.
12. Satter E: Proteus syndrome: 2 case reports and a review of the literature. Cutis 80: 297-302, 2007.
13. Sethi SK, Yadav D, Garg P, Chawla J and Goyal D: A child with mental retardation and asymmetrical hypertrophy of limbs. Eur J Pediatr 170: 813-814, 2011.
14. Ou M, Sun Z, Zhu P, Sun G and Dai Y: Proteus syndrome: A case report and review of the literature. Mol Clin Oncol 6: 381-383, 2017.
15. Bialer MG, Riedy MJ and Wilson WG: Proteus syndrome versus bannayan-zonana syndrome: A problem in differential diagnosis. Eur J Pediatr 148: 122-125, 1988.
16. Haga N, Nakamura K, Taniguchi K and Nakamura S: Enchondromatosis with features of dysspondyloenchondromatosis and maffucci syndrome. Clin Dysmorphol 7: 65-68, 1998.
17. Klein C, Delcourt T, Salon A, Finidori G, Glorion C and Pannier S: Surgical treatment of enchondromas of the hand during childhood in ollier disease. J Hand Surg Am 43: 946.e1-946.e5, 2018.
18. Krengel S, Fustes-Morales A, Carrasco D, Vázquez M, Durán-McKinster C and Ruiz-Maldonado R: Macrodactyly: Report of eight cases and review of the literature. Pediatr Dermatol 17: 270-276, 2000.
19. Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, Turner J, Cannons JL, Bick D, Blakemore L, *et al*: A mosaic activating mutation in AKT1 associated with the proteus syndrome. N Engl J Med 365: 611-619, 2011.
20. Zhou X, Hampel H, Thiele H, Gorlin RJ, Hennekam RC, Parisi M, Winter RM and Eng C: Association of germline mutation in the PTEN tumour suppressor gene and proteus and proteus-like syndromes. Lancet 358: 210-211, 2001.
21. Smith JM, Kirk EP, Theodosopoulos G, Marshall GM, Walker J, Rogers M, Field M, Brereton JJ and Marsh DJ: Germline mutation of the tumour suppressor PTEN in proteus syndrome. J Med Genet 39: 937-940, 2002.
22. Caux F, Plauchu H, Chibon F, Faivre L, Fain O, Vabres P, Bonnet F, Selma ZB, Laroche L, Gérard M and Longy M: Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) syndrome is related to mosaic PTEN nullizygosity. Eur J Hum Genet 15: 767-773, 2007.
23. Loffeld A, McLellan NJ, Cole T and Moss C: Type 2 segmental cowden disease vs. proteus syndrome: Reply from authors. Br J Dermatol 158: 410-411, 2008.
24. Happle R: Lethal genes surviving by mosaicism: A possible explanation for sporadic birth defects involving the skin. J Am Acad Dermatol 16: 899-906, 1987.
25. Alves C, Acosta AX and Toralles MB: Proteus syndrome: Clinical diagnosis of a series of cases. Indian J Endocrinol Metab 17: 1053-1056, 2013.
26. Nguyen D, Turner JT, Olsen C, Biesecker LG and Darling TN: Cutaneous manifestations of proteus syndrome: Correlations with general clinical severity. Arch Dermatol 140: 947-953, 2004.
27. Talari K, Subbanna PK, Amalnath D and Suri SD: Proteus syndrome: A rare case report. Indian J Hum Genet 18: 356-358, 2012.
28. Thomason JL, Abramowsky CR, Rickets RR, Culbertson JH, Clifton MS and Shehata BM: Proteus syndrome: Three case reports with a review of the literature. Fetal Pediatr Pathol 31: 145-153, 2012.
29. Angurana SK, Angurana RS, Panigrahi I and Marwaha RK: Proteus syndrome: Clinical profile of six patients and review of literature. Indian J Hum Genet 19: 202-206, 2013.
30. Li Z, Shen J and Liang J: Thoracolumbar scoliosis in a patient with proteus syndrome: A case report and literature review. Medicine (Baltimore) 94: e360, 2015.
31. Downey Carmona FJ, Lagares A, Farrington-Rueda D and Lirola-Criado J: Island nail flap in the treatment of foot macrodactyly of the first ray in children: Report of two cases. J Child Orthop 9: 281-285, 2015.
32. Wu J, Wang Q, Cui P, Wu X and Yan Z: Recurrent cerebriform connective tissue nevus on the foot of a patient with Proteus syndrome. Cutis 98: E16-E19, 2016.
33. Rocha RCC, Estrella MPS, Amaral DMD, Barbosa AM and Abreu MAM: Proteus syndrome. An Bras Dermatol 92: 717-720, 2017.
34. Vestita M, Filoni A, Arpaia N, Ettorre G and Bonamonte D: Case report: 'Incognito' proteus syndrome. F1000Res 7: 228-236, 2018.