

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

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**Abstract.** Proteus syndrome is a rare complex syndrome involving clinical presentation with atypical skeletal growth. Only a limited number of cases with this syndrome have been reported in the literature to date. We herein report the case of a Chinese male patient with Proteus syndrome and review the clinical and molecular characteristics of this disease. The patient was a 34-year-old man with clinical manifestations suggestive of the Proteus syndrome, including mosaic distribution of the lesions, sporadic occurrence, progressive course, disproportionate overgrowth of the legs, epidermal nevi, lipomas, venous malformations and characteristic facial phenotype. Genetic mosaicism, such as mutations involving the phosphoinositide 3 kinase-AKT pathway in the affected tissues, may be important causes of Proteus syndrome. In the present case, samples from the affected tissues were collected from the patient and were further analyzed using whole-exome sequencing. However, no mutation of the genes reportedly associated with Proteus syndrome was identified in the affected tissues. Proteus syndrome is a complex mosaic disorder with a number of variable characteristics. Although activating AKT1 mutations have been found to be associated with this disorder, the molecular etiology remains to be fully elucidated and diagnostic criteria must be established in the clinical setting.

## Introduction

Proteus syndrome is an extremely rare complex disorder characterized by patchy or mosaic postnatal overgrowth of different body parts (1). Proteus syndrome was first described by Cohen and Hayden in 1979 (2), with an estimated prevalence of <1/1,000,000 live births (3,4). The onset may involve any site of the body and typically occurs during infancy. The severity of Proteus syndrome has been found to vary among different affected individuals, and commonly affected tissues include the skin, connective tissue and bone, central nervous system and eye (5). The affected tissues vary widely regarding the extent of the involvement and the severity in different patients, and they may be divided into four main categories, namely soft tissue tumors, vascular anomalies, macrodactyly and histopathological characteristics (6). The etiology of Proteus syndrome has not been fully elucidated, but somatic genetic alterations, such as AKT somatic mutations, in the affected tissue may be the major causative factor. This is the case report of a Chinese male patient with Proteus syndrome, with a review of the literature on the molecular pathology underlying this disorder.

## Case report

A 34-year-old man was admitted to Shenzhen People's Hospital for treatment of progressive postnatal overgrowth and skin problems mainly involving the limbs and hip. The patient's parents had observed asymmetric overgrowth of the lower limbs during childhood, but no systemic treatment was performed. On physical examination, there was an obvious discrepancy in the length of the legs; in addition, the left lower limb was enlarged and covered by an irregular red-brown plaque (Fig. 1A). Asymmetric growth of the upper limbs was also observed, with the right forearm, which was covered by an irregular epidermal nevus, being larger compared with the left forearm. The structure of the right hand was also clearly affected and the middle and index fingers could not be freely extended; in addition, certain areas of the neck, abdomen and back were covered by a red-brown irregular plaque with hyperpigmented borders (Fig. 1B and C); subcutaneous lipomas were also present. Affected tissue samples were collected from the patient's back for further molecular biological analysis by whole-exome sequencing, as previously described (7). Briefly,

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the whole exome of affected and control tissues was analyzed by high-throughput sequencing. Quality control and basic filtering were performed, and the 90-bp paired-end sequence reads were aligned and used for variant calling. A total of 381 variants were found after the variants were filtered. However, no mutation reportedly associated with the Proteus syndrome was identified. The patient also presented with hematochezia, and a multislice spiral CT revealed multiple hemangioma-like lesions of the large intestinal mucosa and systemic vascular disease (Fig. 2). The patient refused surgery due to the high cost of the treatment and the associated surgical risk, and symptomatic treatment was instead administered to control the skin and gastrointestinal symptoms. The treatment included topical mupirocin for a concurrent infection of the skin lesions on the left lower limb, and oral levofloxacin for the gastrointestinal problems. On the last follow-up, in November 25, 2016, the condition of the patient remained stable; the skin and gastrointestinal symptoms were partly controlled and there was no obvious disease progression.

Written informed consent was obtained from the patient regarding the publication of the case details and associated images.

## Discussion

The exact cause of Proteus syndrome remains unclear, although AKT1 mutations were recently identified as an important cause of this uncommon disease. The Proteus syndrome is a relative rare and complex disease, which is characterized by partial gigantism of the limbs, lipomas, varicosities and verrucous epidermal nevi. After this type of disease was first reported in 1979 (2), similar cases were described by Wiedemann *et al* in 1983 (8); however, only a limited number of cases of the Proteus syndrome have been reported to date. The treatment of Proteus syndrome is challenging, and multiple orthopedic procedures have been attempted in the clinical setting to control abnormal overgrowth; however, patients with this syndrome may suffer severe cosmetic and functional consequences, even with aggressive treatment (4).

Although diagnostic criteria for the Proteus syndrome have been established, the variable phenotype may be a major cause of misdiagnosis. According to the diagnostic criteria revised by Turner *et al* in 2004 (9), each of the general criteria and some of the specific criteria should be present to establish the diagnosis of Proteus syndrome. In the present case, the diagnosis of the Proteus syndrome was based on the presence of 3 of the major criteria, namely mosaic distribution of the lesions, sporadic occurrence and progressive course; and 5 of the specific criteria, namely disproportionate overgrowth of the left leg and epidermal nevi on some areas of the neck, abdomen and back (category B), lipomas, venous malformation and facial phenotype (category C).

Given the high complexity of the clinical characteristics of the Proteus syndrome, the hypothesis of somatic mosaicism underlying this syndrome is important. Based on this hypothesis, Proteus syndrome may develop from certain postzygotic mutations. It was recently indicated that mutations causing dysfunction of the phosphoinositide 3 kinase (PI3K)-AKT pathway, such as phosphatase and tensin homolog (PTEN) and AKT1 mutations, may be important causes of the Proteus



Figure 1. Clinical presentation of a patient with Proteus syndrome. (A) Asymmetric overgrowth of the lower limbs; (B) red-brown irregular plaque with hyperpigmented borders covering the back and buttocks; (C) asymmetric growth of the hands.

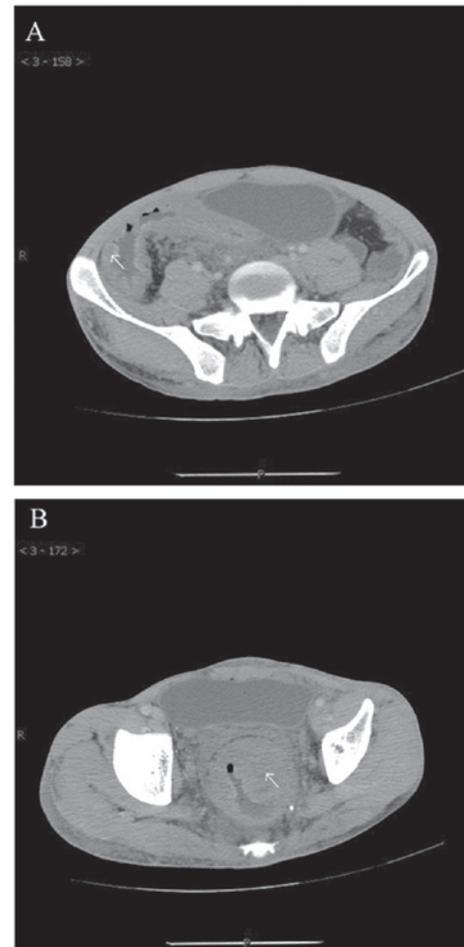


Figure 2. Hemangioma-like lesions of the large intestinal mucosa detected on multislice spiral computed tomography (arrows). Lesions were identified in the (A) colon and (B) rectum.

syndrome (10). However, there is a controversial association between PTEN mutations and the clinical characteristics

of the Proteus syndrome, and certain affected individuals harboring somatic PTEN mutations and clinical characteristics such as segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevi, were diagnosed with the SOLAMEN or the Cowden syndromes (11,12). Considering the clinical characteristics and gene function of PTEN, these three syndromes may belong to the same class of disorders. In 2011, Biesecker (4) identified the genetic basis of Proteus syndrome through analysis of 12 samples of exomes obtained from 6 patients with Proteus syndrome using exome sequencing; additional cases of validation confirmed that somatic mutations in AKT1 were an important cause of Proteus syndrome (10). However, no mutation in the reported Proteus syndrome-associated genes, including AKT1, PTEN or PIK3CA, was found by exome sequencing in our case, which was similar to 3 of the 29 individuals with Proteus syndrome described by Biesecker. It is likely that some mutations in unknown genes may contribute to the development of Proteus syndrome, but further investigation is required.

Considering the severe complications of the Proteus syndrome, it is necessary to diagnose this disorder earlier in childhood, and remain alert regarding potential tumor development in such patients, in order to improve their quality of life. In addition, in the majority of patients, Proteus syndrome may be caused by mutations in certain known genes, and genetic examination of the family members of patients with the syndrome may be performed, which may prove to be valuable for variant filtering and identification of disease-related mutations.

In summary, Proteus syndrome is a relatively recently described and complex disease with a variable phenotype, and its diagnosis is challenging. Although AKT1 mutations have been identified as a cause of Proteus syndrome, the precise pathogenesis and etiology of this syndrome require further investigation.

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