Proteus syndrome: a case report and a case study review in China

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Abstract

Proteus syndrome (PS) is a rare and sporadic disorder characterized by overgrowth of multiple tissues and a propensity to develop particular neoplasms. The clinical manifestations of PS include macrodactyly, vertebral abnormalities, asymmetric limb overgrowth and length discrepancy, hyperostosis, abnormal and asymmetric fat distribution, asymmetric muscle development, connective tissue nevi, and vascular malformations. We report a 16-year old female patient who manifested a number of these complications and review the Chinese literature about the diagnosis, natural history, and management of PS.

Introduction

The malformations in PS can involve skin, subcutaneous tissue, connective tissue (including bone), the central nervous system, and viscera. The main clinical manifestations of PS include hemihypertrophic macrodactyly, subcutaneous tumors, palmar and metatarsal cerebriform connective tissue nevi, lipomas, exogenetic bone mamma, epidermal nevi, vascular malformations, lipohypoplasia, and dermalhypoplasia. In this article, we report a PS case that has a number of clinical manifestations, and review the literature on this unique disorder in China.

Case report

A 16-year old Chinese girl was born to non-consanguineous parents. The pregnancy and delivery were uneventful. Her mother denied any drug use, radiation exposure, or infections during pregnancy. She presented to our institute at the age of 16 with facial dysmorphism and verrucous hyperplasia on the right side of her body. She was born with deafness of the right ear and dry, rough, light brown color pat-

tems on the right trunk. As she grew, the patient developed more abnormalities, including right face, ear, tongue, and lip hyperplasia and overgrowth. The skin of the right trunk thickened and darkened, as the left side remained normal. Her parents, 3 sisters and brother are all normal, and there was no other similar disorder in her family.

Physical examination

The patient was noted to have normal intelligence. Her height and weight were 153 cm and 44 kg, respectively. Her vital signs were within normal limits. The patient showed several anomalies. There was hemihypertrophy involving the entire right side of the head, including the skull, face, ear, palate, tongue, lip and neck. There was an epidermal nevus on the right side of the body, showing general cornification pachydermia. Hyperpigmented swirled and linear skin lesions were present on the right side of the neck and trunk, and verrucous epidermal nevi were seen on the right side of neck. She had malocclusion of the teeth, papillomatus hyperplasia of the tongue, hypertrophy of the right auricle, obstruction of the right auditory meatus, and a vascular malformation and lipomas on the right side of the face. The distal right manihpalanx was enlarged and hammer-like. The right plan-
ta had an amber hyperplastic plaque that was moderately hard in texture and lacked pain sensation (Figures 1 and 2).

Laboratory and auxiliary examination

Computer tomography scan of the patient’s head and face showed a large lipoma in the right face, but there were no abnormalities of the brain. Plain radiographs showed hyperplasia and hypertrophy of the jaw bone. There was a mild protrusion on the side of the thorax and the left tibia was mildly thickened. Electrocardiography was within normal limits. Ultrasounds for the other organs, such as liver, kidney, spleen, pancreas, uterus and both adnexa, were all within normal limits. The histopathological changes in the epi-
dermis were hyperplastic and affected chiefly the stratum corneum and stratum malpighii. Evaluation of the firm nodule adjacent to the right nasal ala revealed dense collagen consistent with a connective tissue nevus or linear verrucous epidermal nevus.

Discussion

Etiology of Proteus syndrome

The cause of PS is still unknown, but a genetic mutation that is viable only in a mos-
ic state has been postulated. Such a mutation might affect local production or regulation of tissue growth factor receptors. This theory would explain the sporadic nature of the syn-
drome, its occurrence in various ethnic groups and both sexes, and its interindividual variability, as well as the mosaic pattern of lesion distribution in all who are affected.

In recent years, some authors have suggest-
ed that PS may be caused by germline mutations within the PTEN gene. The presence of a germline PTEN mutation in a subset of patients with PS has been confirmed by the...
Identification of a de novo PTEN mutation in a patient with classical Proteus syndrome described by Biesecker et al. 4

Proteus Syndrome

Proteus syndrome (PS) is a rare and sporadic disorder that causes postural overgrowth of multiple tissues in a mosaic pattern. While patients with PS have a variable clinical appearance, they exhibit a defined constellation of skin abnormalities. Various skin abnormalities such as fatty, muscular, and vascular malformations were divided into the following categories: skeletal abnormalities, invasive or slow-growing masses, benign and malignant tumors, and deep venous thrombosis with pulmonary embolism. Progressive skeletal abnormalities such as reduced height, scoliosis, asymmetry of limb length, and limb length discrepancies are the most frequent findings in patients with PS. Other findings include soft-tissue abnormalities such as fatty, muscular, and vascular malformations as well as masses other than fatty, muscular, and vascular malformations. Visceral abnormalities such as splenic, renal, and vascular abnormalities are also frequent. The diagnosis of PS was based on published criteria.

The current situation of investigation on Proteus syndrome in China

All 8 patients reported 11-18 in China had at least 2 different skin abnormalities and had other abnormalities, including lipomas, telangectatic nevi or other vascular lesions, plantar cerebriform connective tissue nevi, or linear epidermal nevi on the palm, forearm, trunk, and face. The diagnosis of PS was based on published criteria.

Table 1. Summary of 8 cases with Proteus syndrome in China.

| Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|--------|--------|--------|--------|--------|--------|--------|--------|
| Sex    | female | female | female | male   | female | male   | female |
| Age    | 30 years | 12 years | 6 years | 16 years | 9 years | 30 years | 28 years |
| Abnormality | Left thumb and leg hemihypertrophy, bone thickening, connective tissue nevi, left first phalanx exogenesis mammillla | Left hand hemihypertrophy, epidermal nevi, fibroelastoma of head and face, aorticopulmonary fistula or window, micromandibular deformity, frontal antrum null development, denis malocclusion, jaw bone exogenesis mammillla | Left limb hemihypertrophy, left hand giant finger, epidermal nevi, left arm angiomma, high arcus palatinus | Right face, ear, tongue, and eotolithum hemihypertrophy, right face lipomas, right face telangiectatic nevi, denises malocclusion, right auditory meatus obstruction, auricularis magnus enlargement, right hyperplasia of parotid gland, epidermal nevi, connective tissue nevi, jaw bone exogenesis mammillla, side protruding thoracic vertebra | Right face and nose hemihypertrophy, epidermal nevi, connective tissue nevi, bone thickening | Left leg hemihypertrophy, both lower extremity venous malformation, connective tissue nevi, bone length discrepancy | Left face and head hemihypertrophy, connective tissue nevi, fibrolipoma, sebaceous cyst, bone thickening, limb length discrepancy | Left finger and right foot hemihypertrophy, right lower extremity venous malformations, epidermal nevi, giant hemangiomas of the spleen |
nevi were examined histopathologically in all 8 patients (Table 1).

The reported cases were 6 females and 2 males; the youngest was six years old and the oldest was 30 years old. That only 8 cases have been reported in China suggests that many cases of PS may go unrecognized. China, as the most populated country on the globe at 1.2 billion people, should have more cases than have already been reported. The problem might be that both the clinical manifestations and diagnostic criteria are not familiar to dermatologists. Moreover, medical services are not as accessible to citizens because of China’s status as a developing country. For these reasons, many cases may have been misdiagnosed or undiagnosed.

Although progress is being made in the clinical understanding of PS, much remains to be done. The existence of numerous case reports of patients who do not meet current clinical diagnostic criteria generates confusion about the natural history, the range of manifestations, and effective management techniques for what is now considered to be “true” PS.

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