Unilateral hypertrophic skin lesions, hemimegalencephaly, and meningioma: The many faces of Proteus syndrome

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ABSTRACT

Proteus syndrome is a rare condition with a wide spectrum of abnormalities. It is characterized by hamartomatous malformations involving multiple organs. Serious complications may ensue, such as pulmonary embolism, cystic lung disease, and various neoplasms such as parotid adenomas, ovarian cystadenomas, and meningiomas. We report here a case of Proteus syndrome in a 21-year-old woman who had facial hemihypertrophy, cerebriform plantar hyperplasia, hemimegalencephaly, and meningioma for the rarity of the entity.

Key words: Collagenoma, hemimegalencephaly, meningioma, Proteus syndrome

INTRODUCTION

Proteus syndrome is a hamartomatous disorder characterized by focal overgrowths that can involve any structure of the body giving rise to a wide spectrum of clinical manifestations.[1] It is a complex developmental abnormality that possibly reflects somatic mosaicism for a mutation that would be lethal in a non-mosaic state.[2] Proteus syndrome is believed to be exceedingly rare, with less than 100 confirmed cases reported worldwide[3] with an estimated incidence of less than 1 case per 1,000,000 live births. Skin changes in Proteus syndrome include cerebriform connective tissue nevi, epidermal nevi, vascular malformations, lipomas, lipohypoplasia, and dermal hypoplasia.[4] Other systems that may be involved are the musculoskeletal, eye, venous, pulmonary, and the central nervous systems.[5] Only six cases of Proteus syndrome with meningioma[3] have been reported in the literature till date, the paucity of which has prompted us to present this case.

CASE REPORT

A 21-year-old woman presented with asymmetry of face and limbs and gross thickening of palmoplantar skin. The lesions were asymptomatic and began to appear at three years of age. The lesions evolved gradually to attain the present dimensions. The patient was born of a non-consanguineous parentage, with no family history of similar abnormalities. She had undergone bilateral salpingo-oophorectomy at the age of 11 years for multiple ovarian cysts, resulting in primary amenorrhea. Her past medical history was otherwise unremarkable.

On examination, we saw asymmetrical overgrowth on the right side of her head, face, and upper and lower limbs. There was a clear line of demarcation separating the hypertrophic right side from the normal left side of her face [Figure 1]. Ptosis of the right eyelid and proptosis of the right eye was noted. Secondary sexual characteristics were poorly developed corresponding to Tanner stage II. There was macrodactyly of hand and feet and cerebriform thickening of the right palmar and plantar skin [Figures 2, and 3]. No bony swellings or subcutaneous masses were noticed. Histology of a biopsy specimen from the plantar skin revealed a normal epidermis, thick bundles of collagen in the papillary and reticular dermis, consistent with connective tissue nevus [Figures 4, and 5]. There were no vascular malformations or prominent vessels in the course of the limbs. No alopecia, café au lait macules, or neurofibromas were noted.

Investigations revealed a normal routine hemogram and coagulation profile. Thyroid

Figure 1: Facial asymmetry of right side with ptosis of right eyelid, proptosis, and narrowing of palpebral fissure

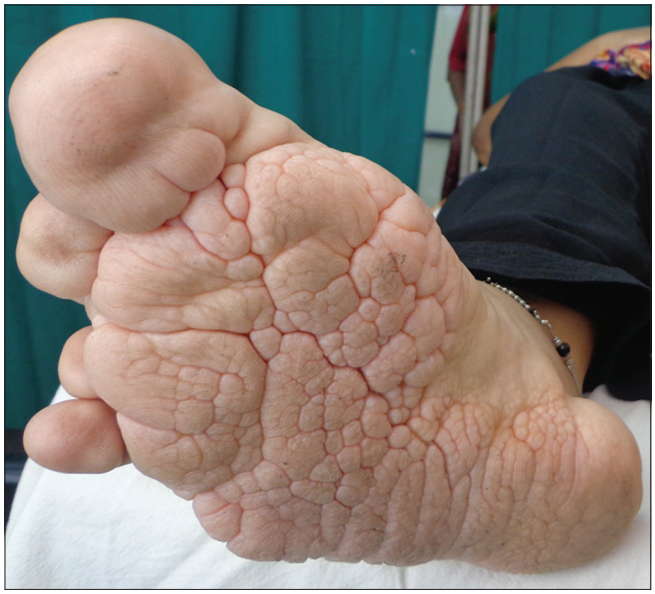

Figure 3: Cerebriform plantar hyperplasia of right foot

profile was normal. Plain skiagraphy revealed thoracic scoliosis, hypertrophy of bones of right upper and lower limbs, and macrodactyly. Computed tomography scan of whole abdomen showed absence of ovaries on both sides. No tumors of the colon or rectum were seen. Magnetic resonance imaging of the

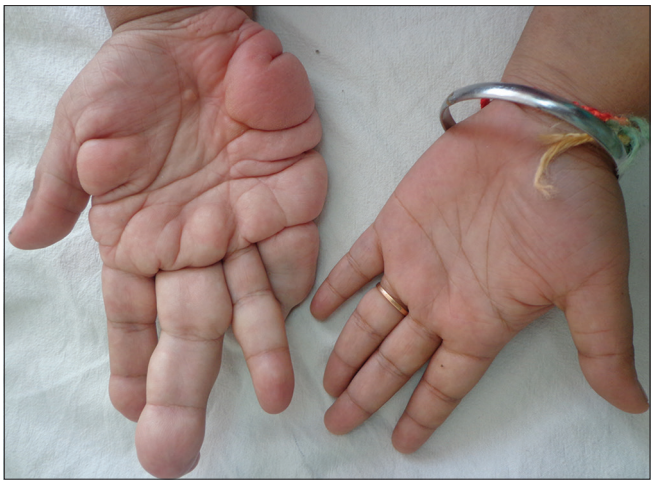

Figure 2: Palmar thickening of right hand with macrodactyly

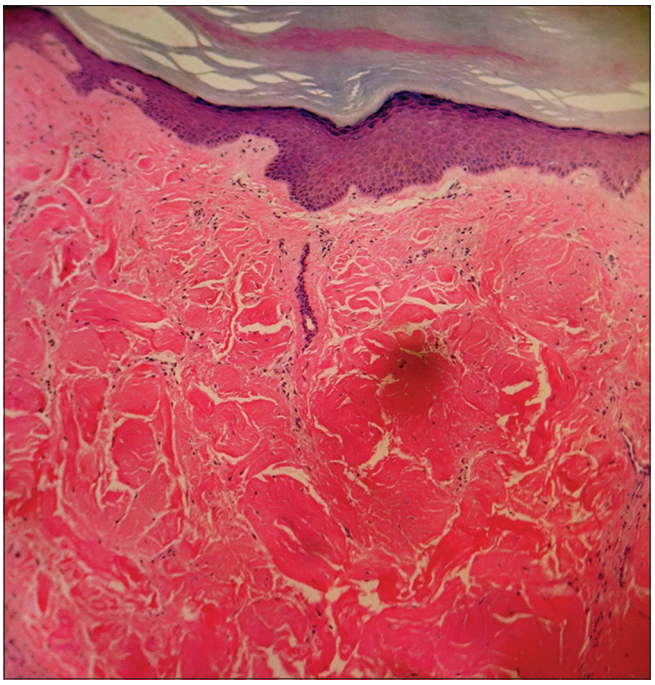

Figure 4: Histopathology of palmar skin revealing increased collagen in the dermis (hematoxylin and eosin, ×100)

brain revealed hemimegalencephaly, fibrous dysplasia, and an extra-axial space occupying lesion in the right anterior middle cranial fossa, suggestive of meningioma [Figure 6].

Based on the distinctive clinical, radiological, and histopathological findings, a diagnosis of Proteus syndrome was made and the patient referred to the neurosurgeon and plastic surgeon for tumor excision and correction of facial disfigurement, respectively.

DISCUSSION

The term Proteus syndrome was coined by Wiedemann in

1983, after the mythical Greek god Proteus, whose name means "the polymorphous,", who could change shape to avoid capture.[6] The unique feature of Proteus syndrome is the morphologic variability characterized by abnormalities in growth (asymmetric overgrowth, increased stature, macrodactyly, soft tissue hypertrophy, elongated neck, macrocephaly), musculoskeletal (hemihypertrophy, bony prominences, ankle ankylosis, craniosynostosis, mandibular prognathia, scoliosis, pectus excavatum, thinning of the cortical layer of long bones), eyes (ptosis, strabismus, nystagmus, myopia, colobomas, cataracts, epibulbar dermoids, blue sclera), central nervous system (seizures, mental retardation,), vascular malformations (venous, arterial, capillary or a combination of these, port wine stain) and the lung (cysts).[5] Tumor-like monomorphic adenomas, meningiomas, and ovarian cystadenomas may also be present.[3]

The following are the three general criteria necessary for the clinical diagnosis without regard to specific clinical features:[3]

- Lesions follow a mosaic distribution or pattern
- Problems follow a progressive course
- The disorder appears to be sporadic (i.e., not inherited).

Specific criteria are listed in Table 1. For diagnosis, one criterion from category A or two from category B, or three from category C must be fulfilled. Our patient had one category A, two category B, and one category C features, thus confirming the diagnosis of Proteus syndrome.

The clinical differentials of Proteus syndrome include Klippel-Trenaunay syndrome, Bannayan-Riley syndrome (macrocephaly, capillary malformation, polyposis coli, and Hashimoto thyroiditis), encephalocraniocutaneous syndrome (nevus psiloliparus consisted of large, slightly protuberant usually unilateral soft masses on scalp with complete alopecia, skin colored papular eruptions on face with some bony and eye and neurological changes), hemihyperplasia syndrome (multiple lipomas, cutaneous vascular overgrowth without any progressive overgrowth), and neurofibromatosis (macrocephaly, café au lait macules, and neurofibromas).[2]

Neurological manifestations in Proteus syndrome are characterized by megalencephaly, mental retardation, seizures, and meningiomas.[7] Asahima *et al*. reported a case of Proteus syndrome with multiple spinal meningiomas and lung cysts,[8]

Table 1: Specific criteria for diagnosis of Proteus syndrome[3]

Category	Features
A	Connective tissue nevus
B	Epidermal nevus
	Bilateral ovarian cystadenomas or a parotid monomorphic adenoma in a patient younger than 20 years
	Disproportionate overgrowth of limbs, skull, viscera, vertebra, and external auditory meatus
C	Lipomas or focal atrophy of adipose tissue
	Capillary, venous, or lymphatic malformation
	Facial features including dolichocephaly, a long face, down-slanting palpebrae, ptosis, depressed nasal bridge, anteverted nares, and open mouth position while at rest

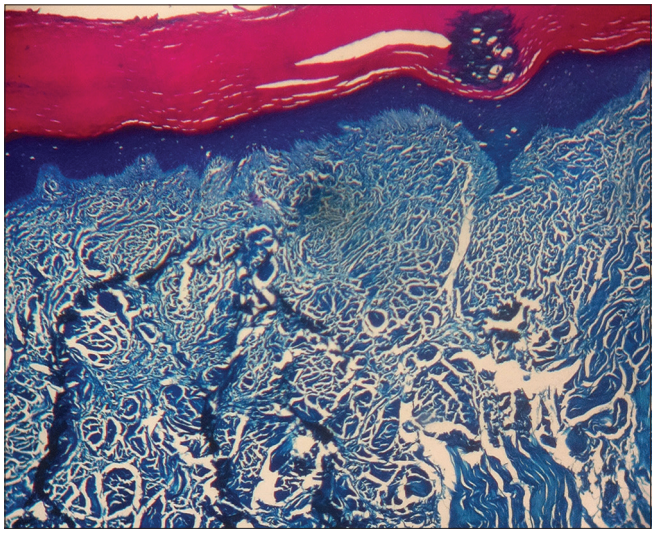

Figure 5: Thick bundles of collagen in the dermis (stained blue by Masson's trichrome staining ×50)

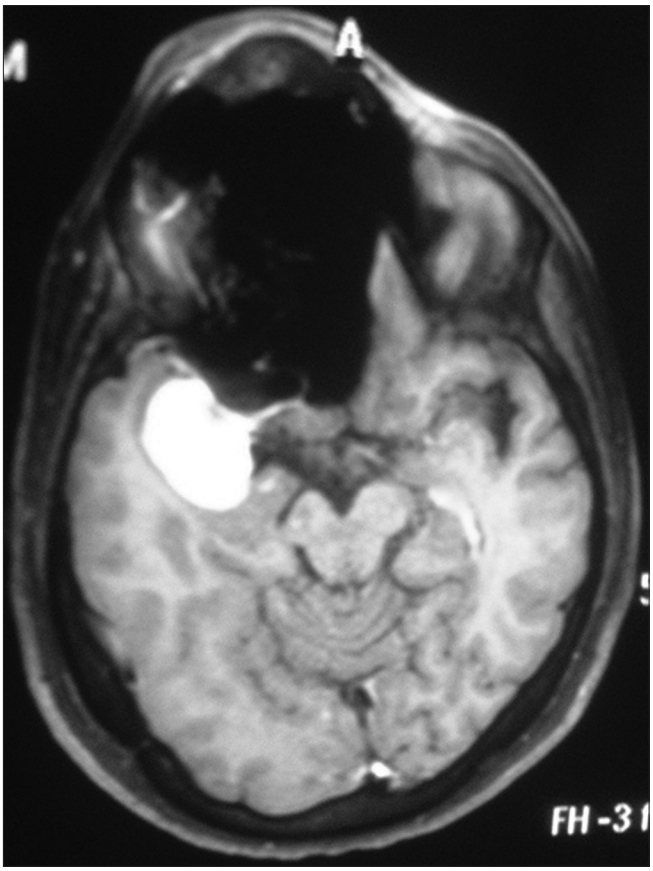

Figure 6: Magnetic resonance imaging brain showing extra-axial meningioma of right anterior middle cranial fossa

whereas Horie *et al*. reported multiple intracranial meningiomas from an autopsy case of Proteus syndrome.[9] Gilbert *et al*. have also reported multiple meningiomas, craniofacial hyperostosis, and retinal abnormalities in Proteus syndrome.[10]

Our patient presented with characteristic features of Proteus syndrome along with extra-axial meningioma and primary amenorrhea. Her lack of menarche was possibly due to bilateral salpingo-oophorectomy for ovarian cysts. Both meningiomas and ovarian cysts are uncommon neoplasms associated with Proteus syndrome.[3]

The mainstay of treatment for Proteus syndrome includes early identification of serious medical problems and the use of prophylactic and symptomatic treatment. Laser treatment is useful for removing cutaneous vascular markings and malformations, such as port wine stains and capillary hemangiomas. Leg length discrepancy can create a host of secondary morbidities and needs to be addressed by an experienced orthopaedist. Aggressive management of the thrombosis may be lifesaving in patients who present with calf or leg pain, a palpable cord, and shortness of breath or respiratory distress. Severe disfigurement and social stigmatization are additional challenges that must be addressed.[7]

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