A Limited Form of Proteus Syndrome With Bilateral Plantar Cerebriform Collagenomas and Varicose Veins Secondary to a Mosaic AKT1 Mutation

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Proteus syndrome is a rare overgrowth disorder that is caused by somatic mosaicism in the AKT1 gene (OMIM 176920). It is characterized by disproportionate and progressive overgrowth affecting multiple tissues including bone, soft tissue, and skin. The 4 common skin lesions seen in this condition include epidermal nevi, vascular malformations, lipomas, and the characteristic plantar cerebriform collagenoma (also known as a cerebriform connective tissue nevus). Affected individuals typically have striking asymmetrical skeletal enlargement that results in substantial disfigurement and loss of function. Because of the progressive nature and variability of the disorder, making a clinical diagnosis of Proteus syndrome can be difficult. We describe a patient with a very mild form of Proteus syndrome whose manifestations do not meet the published clinical criteria, which raises important questions about diagnosing mosaic disorders.

Report of a Case

A 33-year-old man was seen for cerebriform tumors over the plantar surfaces of both feet (Figure 1A). The lesions were first noticed around the age of 4 years and grew progressively during childhood and adolescence. Overgrowth under his toes led to problems with walking, and he underwent debulking surgery at age 16 years. During adulthood there has been no further enlargement, and he does not experience any functional impairment. He also has severe varicose veins in his legs, which similarly developed in early childhood. Venous duplex ultrasonography at age 16 years showed severely dilated varicose veins as a result of valvular reflux at the saphenofemoral junction, and he underwent stripping of the long saphenous veins. There is no family history of plantar cerebriform collagenomas or varicose veins occurring in childhood. Examination showed asymmetrical, soft, cerebriform plaques with prominent gyriform-like sulci over the plantar surfaces of both feet (Figure 1B). There were prominent varicose veins in both legs. He had no clinical evidence of skeletal abnormalities, dysregulation of adipose tissue, or of any other notable skin lesion.

A skin biopsy sample taken from the left sole showed a markedly thickened dermis, consisting of thick collagen fibers arranged in a haphazard orientation (Figure 2A). Elastic-van Gieson staining demonstrated a reduction in elastic fibers in the reticular dermis, with fragmented elastic fibers seen...
on high power. These histological findings are consistent with a collagenoma. In addition, large-caliber, irregular thick-walled vessels with valves were seen at the interface of the deep dermis and subcutaneous tissue. Their appearances, together with their staining pattern on the elastic–van Gieson stain (Figure 2B) and lack of immunostaining with D2-40, suggest that they represent veins. To further investigate his varicose veins, he underwent a magnetic resonance venogram, which showed marked dilatation of the superficial and deep perforator veins in the legs and feet, consistent with deep venous malformations. Radiographs of the limbs and feet showed no evidence of skeletal abnormalities.

To assess for the AKT1 c.49G>A mutation in this patient, DNA was isolated from a collagenoma skin biopsy and from peripheral blood, and the mutation level was assessed using a custom-designed, quantitative restriction enzyme assay as described previously. The mutation was found at a level of 3% in the collagenoma DNA sample but was not detected in the peripheral blood sample, consistent with somatic mosaicism.

Discussion

Proteus syndrome is a rare, sporadic disorder (incidence of <1 case per 1 million population) characterized by patchy or segmental overgrowth of diverse tissues of all germ layers, most commonly affecting the skeleton, skin, adipose tissue, and central nervous system. The condition is named after the mythical Greek sea-god who was able to assume many forms. Somatic mosaicism was hypothesized as the cause because of the sporadic occurrence, mosaic distribution of lesions, and variable extent of involvement. Joseph Merrick, a man who lived in the late 19th century and was known as the Elephant Man, is thought to have had Proteus syndrome.

The plantar cerebriform collagenoma is a connective tissue nevus associated with a proliferation of collagen in the dermis that leads to a distinctive cerebriform appearance. It is the most characteristic skin finding in Proteus syndrome, although it is not seen in all patients. The typical site of involvement is the plantar aspect of the feet, but it can also develop over the palms and more rarely over the trunk, arms, and face. In contrast to epidermal nevi and vascular malformations, which are usually seen in the first month of life, the plantar cerebriform collagenoma usually develops during the first 2 years of life. It is an extremely rare cutaneous finding, and because of its specificity for Proteus syndrome, it is the only category A sign (cerebriform connective tissue nevus) in the diagnostic criteria. Some authors have considered the plantar cerebriform collagenoma to be pathognomonic for Proteus syndrome. However, there are a few reports of isolated plantar cerebriform collagenoma occurring in the absence of any other feature of Proteus syndrome, with all but 1 case displaying small unilateral plaques or nodules. Most of these patients did not have the typical cerebriform appearance seen in Proteus syndrome. Of note, the only patient with bilateral plantar...
involvement\textsuperscript{6} was later found to have Proteus syndrome.\textsuperscript{5} All of these reports preceded the identification of the genetic basis of Proteus syndrome, which was found to be a somatic activating mutation in the oncogene AKT1.\textsuperscript{1} This gene is involved in the PI3K-AKT-mTOR signaling pathway and encodes an enzyme mediating cell proliferation and apoptosis. Mutations in several genes involved in the PI3K-AKT-mTOR pathway that lead to upregulation are now known to be responsible for a number of hamartoma or overgrowth syndromes (Figure 3). In Proteus syndrome, the constitutive activation of the AKT1 protein is thought to underlie the overgrowth and tumor susceptibility seen in affected individuals.\textsuperscript{1} To date, all patients with a clinical diagnosis of Proteus syndrome have the same c.49G>A, p.Glu17Lys AKT1 mutation.

Prior to the discovery of the molecular basis of Proteus syndrome, it was necessary to use only clinical features to diagnose the disorder. This led to a substantial degree of confusion and misdiagnosis, which was addressed by formal diagnostic criteria, which were updated in 2006 (Box).\textsuperscript{14} The present patient does not strictly meet the current diagnostic criteria because he fulfills only 2 of the 3 mandatory general criteria, with features that are mosaic and sporadic in nature but not progressive. Of the specific criteria, his plantar cerebriform collagenoma is a criterion from category A, whereas his varicose veins, which are the result of deep venous malformations, constitute a single criterion from category C. Therefore, he meets the specific criteria but not the mandatory general criteria for a clinical diagnosis. Despite this, the unusual clinical features and development in early childhood raised our suspicion that this could be a \textit{forme fruste} of Proteus syndrome. This was confirmed by the finding of the c.49G>A, p.Glu17Lys AKT1 mutation in lesional skin but not in his blood. The limited involvement in this patient suggests that the somatic mutation may have occurred later in fetal development (compared with more typically affected patients) because an early postzygotic mutation would give rise to more extensive abnormal cell lineages.

Conclusions

The results of our analysis suggest that the diagnostic criteria are limited in their ability to account for patients with mild manifestations because progressive changes (the third general criterion) are more applicable to the skeletal system. There is evidence that although the plantar cerebriform collagenoma grows progressively during childhood, it remains stable in adulthood, as seen in the patient reported here.\textsuperscript{15} More generally, the clinical manifestations of patients with mosaic disorders are intrinsically limited by the initial mutational event—if that event occurs early in development and affects many tissues, the manifestations will be widespread and recognizable.\textsuperscript{16} If that event occurs late in development, the manifestations will be more anatomically limited and mild in degree. In fact, it is theoretically possible that a patient could harbor only a few cells or even a single cell with the AKT1 mutation in lesional skin but not in his blood.
c.49G>A p.Glu17Lys mutation, which may have few or no clinical consequences. This then begs the question of what the lower boundary of a clinical diagnosis of Proteus syndrome should be. While it is tempting to fall back entirely on the molecular findings, it would make little sense to give a patient with a small, isolated cerebriform collagenoma and no other manifestations a diagnosis of Proteus syndrome. This same mutation is known to occur as a part of the genomic mutational landscape of a number of cancers including breast, colorectal, and ovarian. Patients with these tumors would clearly not be described as having Proteus syndrome. This issue has also arisen with other genes and phenotypes in dermatology. An example of this that was recently reviewed is the mosaic mutation of the Gly12 residue of HRAS, which has been found in the mosaic state in benign keratinocytic epidermal nevi and bladder cancer and in constitutional or germline state in the congenital malformation disorder Costello syndrome. Again, it would be highly problematic to suggest that patients with only the skin lesion or bladder cancer have Costello syndrome. Therefore, it is clear that our preconceptions about clinical and molecular diagnosis are not readily transferrable from germline to mosaic disorders, and novel approaches may be necessary. In the case of Proteus syndrome and other phenotypes with both germline and mosaic mutations, such efforts to reclassify phenotypic and molecular diagnosis will await more data on the range of these manifestations.

REFERENCES