

Editorial Comment

Proteus Syndrome: Misdiagnosis With *PTEN* Mutations

In this editorial, we briefly (1) define Proteus syndrome; (2) analyze reports of *PTEN* mutations claimed to have “Proteus syndrome” or a “Proteus-like syndrome”; (3) demonstrate the high frequency of misdiagnosis of Proteus syndrome by clinicians less familiar with the disorder; and (4) discuss two series of patients who do meet the diagnostic criteria for Proteus syndrome among whom none have been found to have *PTEN* mutations.

Proteus syndrome is a highly variable disorder with strikingly relentless asymmetric and disproportionate overgrowth of body parts, cerebriform connective tissue nevi, epidermal nevi, dysregulated adipose tissue, and vascular malformations [Cohen and Hayden, 1979; Wiedemann et al., 1983; Cohen et al., 2002]. The cause or causes are unknown. The current working hypothesis is that Proteus syndrome arises from a postzygotic mutation based on (1) mosaic distribution of lesions, (2) sporadic occurrence, (3) exclusively unaffected offspring born to affected individuals, and (4) discordant identical twins [Happle, 1987; Cohen, 1993; Biesecker et al., 1998, 1999; Cohen et al., 2002]. No other model has been proposed that would account for these observations.

For reasons to be explained, we are of critical of (1) reported cases said to have Proteus syndrome with *PTEN* germ line mutations [Zhou et al., 2001; Smith et al., 2002] and (2) reported *PTEN* mutations, using the unhelpful and confounding clinical term “Proteus-like syndrome” [Zhou et al., 2000, 2001]. We do not dispute the *PTEN* mutations found per se, but the clinical diagnosis of Proteus syndrome. Zhou et al. [2000] studied five patients said to have Proteus syndrome and one patient with a “Proteus-like syndrome.” No mutations were found in the five “Proteus syndrome” patients. A germline mutation was found and tissue samples showed loss of heterozygosity in the “Proteus-like” patient. Clinical features included “marked hypertrophy of the right lower extremity in girth and length, pink verrucoid epidermal naevi...with...plaques on the right side of his body, and macrocephaly.” He also had lipomas and “invasive arteriovenous malformations involving the muscles and bones of the entire right lower extremity, pelvis, lower abdomen, and buttocks,

as well as diffuse verrucoid epidermal naevi over his hands, legs, and face.” He developed “progressive heart failure” and also had “hypothyroidism.” Zhou et al. [2000] specifically stated that their patient did not have Proteus syndrome but labeled him as having a “Proteus-like syndrome.”

Zhou et al. [2001] then studied 14 patients from several academic medical centers in the United States and Europe. *PTEN* germline mutations were found in two of nine Proteus syndrome patients said to have met the diagnostic criteria for PS. Three of the five patients with a “Proteus-like syndrome” were also found to have *PTEN* germline mutations.

Zhou et al. [2001] provide insufficient data about their two cases of “Proteus syndrome” to be validated. In their table of listed findings, one patient (their PS2) had insufficient findings for the diagnosis of Proteus syndrome [Biesecker et al., 2001]. More comprehensive clinical data were not available because of issues of informed consent [Biesecker et al., 2001; Eng et al., 2001]. The term “Proteus-like syndrome” applied to 13 patients by Zhou et al. [2001] has already been discussed above.

Smith et al. [2002] reported a *PTEN* mutation in a patient said to have “classical Proteus syndrome.” Findings included an extensive epidermal nevus involving the left arm, hand, chest, and flank; widespread capillary malformations of the chest, abdomen, and right leg; and evidence of disproportionate overgrowth of the right leg.

Many findings reported by Smith et al. [2002] indicate that their patient does not have Proteus syndrome. The following features of their propositus have never been seen in Proteus syndrome patients by us; lipoblastomatosis (not the same as lipomas which their patient also had); multiple sessile polypoid lesions of the jejunum and colon (characteristic of the *PTEN* hamartoma-tumor syndrome); and apparently a true hemangioma in addition to vascular malformations. We are unimpressed by the degree of “disproportionate overgrowth” shown in their patient. The combination of polyposis, lipomas, vascular malformations, and hemangiomas has been reported in the *PTEN* hamartoma-tumor syndrome [Cohen et al., 2002].

We have evaluated over 200 patients claimed to have Proteus syndrome from the literature or from referrals for consultation. This analysis will be published in detail elsewhere [Turner et al., 2003]. Briefly, by applying the published diagnostic criteria for Proteus syndrome [Biesecker et al., 1999], only about half of these patients actually had Proteus syndrome. By using independent

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assessment for each case, the diagnostic criteria were robust and were congruent in well over 95% of the cases [Turner et al., 2003].¹ We conclude that it is common for clinicians who are unfamiliar with the disorder to misdiagnose it. Given this high rate of misdiagnosis of Proteus syndrome, it must be concluded that many patients with this diagnostic label have other conditions.

The difficulty that some physicians have in using the published diagnostic criteria has been misinterpreted by Eng et al. [2001]. We claim here, and have previously stated [Biesecker et al., 2001], that about 50% of patients who carry the diagnosis of Proteus syndrome have some other overgrowth syndrome instead of Proteus syndrome. Eng misinterprets this as “Biesecker and colleagues claim that the diagnostic criteria might be only 50% sensitive” [Eng et al., 2001]. When we say that about 50% of the Proteus diagnoses of other clinicians actually represent patients who have other overgrowth syndromes, this means that the positive predictive value of the diagnostic criteria in their hands is about 0.5, not that the sensitivity is 0.5. We do not encounter instances in which clinicians believe that a patient with overgrowth has a disorder other than Proteus and we conclude that they actually do have Proteus. This suggests that the assignment of a diagnosis by physicians who are not experts on Proteus syndrome has no more value than a coin toss insofar as distinguishing Proteus syndrome from other overgrowth disorders.

In addition, we and others have attempted to confirm the findings of *PTEN* mutations in Proteus syndrome, but these data were negative. In eight cases of Proteus syndrome, Barker et al. [2001] performed *PTEN* mutation analysis by SSCP and found no *PTEN* mutations. In 19 cases of Proteus syndrome, we directly sequenced the *PTEN* gene but found no mutations [Biesecker et al., 2001]. All 27 patients with negative *PTEN* results clearly meet the diagnostic criteria for Proteus syndrome [Biesecker et al., 1999]. Eng et al. [2001] stated that direct sequencing is “around 100%” sensitive for detecting *PTEN* mutations and we have done this for our diagnostically confirmed Proteus syndrome patients with negative results.

The patients described as “Proteus-like” raise another issue. The use of a term such as “Proteus-like syndrome” obscures important phenotypic distinctions of bona fide Proteus syndrome when compared to other overgrowth disorders. An historical example of another poorly chosen name that relied on “similarities” to another condition is male Turner syndrome. The designation was confusing because it suggested that the disorder, now known as Noonan syndrome, could not affect females. In addition, the designation did not further an appreciation for the distinct genetic etiology of the conditions. For similar reasons, we strongly discourage the use of the term “Proteus-like syndrome.”

In conclusion, to date, no reported patient with a *PTEN* mutation has Proteus syndrome. Just saying they

have Proteus syndrome [Eng et al., 2001; Zhou et al., 2001; Smith et al., 2002] does not make it so. We recognize the well-established principle of genetic heterogeneity. This may apply to Proteus syndrome when the cause or causes, unknown at present, become known in the future.

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¹The three of us disagreed on only six literature cases. During a conference call, the six cases were easily resolved; in these instances, one or two of us had missed some key piece of information in the articles in question.