INTRODUCTION

Proteus syndrome is a genetic condition caused by an AKT1 mosaic activating variant, resulting in progressive and asymmetric overgrowth of the skin, soft tissues, bones, and internal organs.1 Skin findings are an important component of Proteus syndrome, including cerebriform connective tissue nevus, epidermal nevus, lipomatous dysregulation (lipomas or lipoatrophy), and vascular malformations.2 Additional associated skin findings include patchy dermal hypoplasia and pigmentary alterations.2,3 We recently documented individuals with Proteus syndrome who had hypertrichosis following the lines of Blaschko.4 Herein, we report another mosaic skin manifestation of Proteus syndrome that involves the pilosebaceous unit.

CASE REPORT

A male adolescent with cutaneous features including cerebriform connective tissue nevus, epidermal nevus, combined venous and capillary malformations, lipomas, and a c.49G>A, p.Glu17Lys variant of AKT1 in affected tissue received a clinical-molecular diagnosis of Proteus syndrome.5 He presented for dermatologic evaluation of acne at age 15 years (Fig 1), which began on his face and spread to the left upper portion of his back. Previous treatments included topical tretinoin, benzoyl peroxide, clindamycin, tazarotene, and oral antibiotics, with limited efficacy.

His physical examination at age 17 years showed scattered comedones and erythematous papules, with some scarring of the face, chest, and upper portion of the back. In addition, there were large inflammatory papules, pustules, and nodules clustered in a blaschkoid distribution along the left upper portion of the back and left side of the neck (Fig 2). There had been no visible skin changes in this area before appearance of acne, documented in clinical photographs obtained annually from age 11 to 13 years. He reported that the hair on the left side of his face was growing more rapidly than on the right side. He had left-sided thoracolumbar scoliosis, overgrowth of the left side of the maxilla, and capillary malformations on the left side of the trunk, and there were varicosities on the legs, which were more prominent on the left leg. He had bilateral cerebriform connective tissue nevus on the soles.
There was an epidermal nevus on his left heel.

His physical examination at age 19 years showed persistent acne on the back (Fig 4) that had improved slightly with oral doxycycline, although significant scarring was present. The possibility of changing to a new oral antibiotic was discussed. The individual subsequently pursued photodynamic therapy, but his linear and disseminated lesions of acne were persistent.

**DISCUSSION**

Several patterns of mosaicism in the skin have been described, including narrow lines of Blaschko, broad lines of Blaschko, checkboard pattern, phylloid pattern, and patchy pattern without midline separation. The acne lesions in this individual consisted of mild disease in a typical distribution on the face and back plus more severe disease on the left upper portion of the back, most consistent with multiple narrow lines of Blaschko. These regions did not show acne or other skin changes at birth or during early childhood. We hypothesize that the blaschkoid, severe acne in this individual represents a mosaic manifestation of Proteus syndrome.

Acne lesions in this individual occurred most notably in a blaschkoid pattern on the left upper portion of the back. Several mosaic manifestations of Proteus syndrome also predominated on his left side, including an epidermal nevus, vascular malformations, maxillary overgrowth, and increased hair growth on the face. The blaschkoid pattern and the shared left-sided predominance suggest that the region of skin with more severe acne may consist of cells affected by the activating \(AKT1\) variant. In Proteus syndrome, the type of skin lesion appears to depend, in part, on which cell lineages are affected by the \(AKT1\) variant. In epidermal nevus, the \(AKT1\) variant is primarily in keratinocytes, whereas in the cerebriform connective tissue nevus, fibroblasts are affected. It is possible that the hair follicles in the region of blaschkoid acne are enriched with cells affected by the \(AKT1\) variant.

In this individual, the blaschkoid acne occurred at puberty on an otherwise clinically silent area of
mosaicism. Unilateral blaschkoid acne lesions with onset at puberty, overlying areas of hypopigmentation, have been reported as a result of a pathogenic variant in \textit{FGFR2}, which is thought to represent mosaic Apert syndrome.\(^8\) Blaschkoid acne superimposed on an epidermal nevus has been reported on the left upper portion of the back of a 13-year-old male adolescent.\(^9\) That individual did not have Proteus syndrome, but it would be interesting to test for the \textit{AKT1} variant in similarly affected people. In the patient described herein, the onset of more severe blaschkoid acne at puberty suggests that there is increased sensitivity of typical factors contributing to acne rather than \textit{AKT1} variant driving acne development on its own.

Acne results from androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles by \textit{Propionibacterium acnes}. An interesting feature in this patient with Proteus syndrome is the absence of concomitant increased hair growth in regions of the back with acne lesions. Hypertrichosis is also an androgen-mediated process and has been shown to follow the lines of Blaschko in Proteus syndrome.\(^4\) The individual did report hypertrichosis and acne on the left side of his face relative to the right, but not on his back.

The multifactorial pathogenesis implicated in this patient’s acne may account for its recalcitrance to treatment. The acne did not respond to multiple, conventional topical or systemic agents. We posit that an AKT inhibitor such as miransertib, which has shown promise in reduction of cerebriform connective tissue nevus,\(^10\) may benefit blaschkoid acne in Proteus syndrome, but this remains to be studied.

In conclusion, mosaicism may affect the pilosebaceous unit and manifest as blaschkoid acne in Proteus syndrome. However, because many individuals receive acne treatment throughout puberty, lesions may not always be apparent. Localized acne following the lines of Blaschko may represent an underreported mosaic phenotype of Proteus syndrome.

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