Segmental epidermal nevus and mucosal neuromas associated with *PIK3CA*-related overgrowth spectrum disorder

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INTRODUCTION

Mosaic and segmental overgrowth syndromes have historically been difficult to delineate and diagnose due to clinical heterogeneity. More recently, the ability to characterize the underlying somatic mutation has helped reclassify these disorders. Several distinct but overlapping conditions and benign lesions have been noted to contain mutations in the *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene, leading to overgrowth.[1]

We present the case of an adult with an uncommon segmental overgrowth disorder with hemifacial overgrowth, linear epidermal nevus, and mucosal neuromas with activating somatic mutations in *PIK3CA*.

Abbreviations used:

PIK3CA:	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PROS:	*PIK3CA*-related overgrowth spectrum
RET:	rearranged during transfection

CASE

A woman in her 20s presented for evaluation and management of a birthmark. She was born with a birthmark on her left cheek, neck, and chest along with thickening of the left cheek and tongue. Prior treatment over 10 years ago included a partial excision of the neck lesion, but she had never had an evaluation for the tongue and cheek changes. Examination was notable for a Blaschko-linear, brown papillomatous plaque on the left ear, cheek, neck, and chest. On the left tongue and buccal cheek, there were fleshy papules and hypertrophy of the left cheek, left tongue, and left upper and lower vermillion lips (Figs 1-3). Histopathology of the brown plaque revealed epidermal acanthosis and papillomatosis consistent with an epidermal nevus, and histopathology of the tongue lesion showed mucosal neuromas. Mutation profiling by massive parallel DNA sequencing of tissue from both the mucosal neuroma and epidermal nevus was positive for an activating E542K mutation in the *PIK3CA* gene with an allele frequency of 15.8%. No other mutations were identified, including any in gene *RET* (rearranged during transfection), leading to a diagnosis of a *PIK3CA*-related overgrowth spectrum (PROS) disorder. Given the association of mucosal neuromas with multiple endocrine neoplasia type 2B, a somatic *RET* mutation was essential to exclude. If present, a segmental form of multiple endocrine neoplasia 2B could carry a risk for associated medullary thyroid cancer. The patient previously had a computer tomography scan and magnetic resonance imaging of the head that both revealed generalized overgrowth of tissue but no lipomatosis.

DISCUSSION

The *PIK3CA* gene encodes a tyrosine kinase, which functions within the AKT—mammalian target of rapamycin pathway, where it has broad

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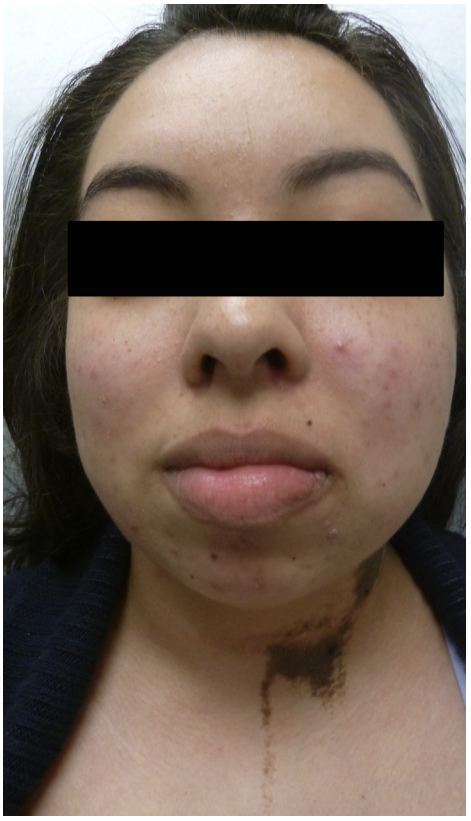

Fig 1. Frontal view showing hemifacial hypertrophy.

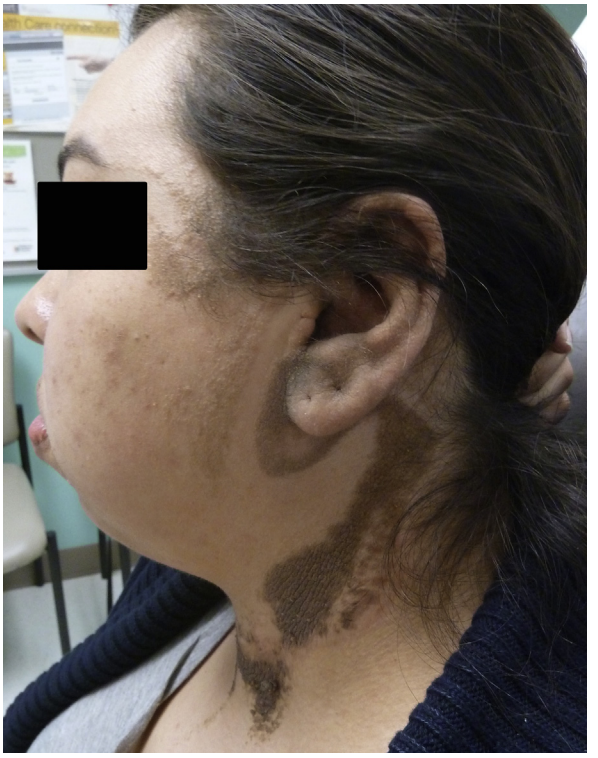

Fig 2. Blaschko-linear epidermal nevus involving left cheek, neck, and chest.

effects on cell growth and migration in many cell types.[2] *PIK3CA*-activating mutations are associated with several overgrowth syndromes including congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome, fibroadipose hyperplasia or overgrowth, hemihyperplasia multiple lipomatosis, fibroadipose-infiltrating lipomatosis, megalencephaly-capillary malformation, and dysplastic megalencephaly. *PIK3CA* mutations also have been described in association with focal benign tumors, including seborrheic keratoses, epidermal nevi, and benign lichenoid keratoses.[1] Confusion exists, considering several overgrowth syndromes have been defined in the literature on the basis of clinical features, but underlying *PIK3CA* mutations vary and have different manifestations, depending on when mutations occur in embryogenesis. Prior reports exist of facial-infiltrating lipomatosis, a rare congenital syndrome associated with hemifacial overgrowth, bony abnormalities, mucosal neuromas, and epidermal nevi in some cases. These cases have similar features of epidermal nevi and mucosal neuromas as in our case. Somatic mutations in *PIK3CA* have recently been described in this disorder,[1,3-5] which is now considered to be within the PROS disorders.[1] One previous case of segmental epidermal nevus and segmental mucosal neuromas has been described, which was also negative for *RET*, but was not evaluated for *PIK3CA* mutations.[6]

Diagnostic criteria for PROS have recently been described. Criteria include the presence of somatic *PIK3CA* mutations, congenital or early disease onset, overgrowth of tissue that appears sporadic and mosaic, and features of ≥ 2 of the following: overgrowth of adipose, muscle, nerve, or skeletal tissue; vascular malformations; and epidermal nevi.[1] With overgrowth of nerve and skeletal tissue and epidermal nevi, our patient met all required criteria.

Several methods exist to evaluate for *PIK3CA* mutations in the tissue, including digital droplet PCR, snapshot assay, Sanger sequencing, qBiomarker array, MassARRAY system, next-generation sequencing, and custom restriction fragment length polymorphism. Detection levels and the level of mosaicism vary widely, so a negative result must be interpreted with caution.[1] The patient's E542K mutation has been described in PROS disorders. Further imaging is recommended in infants and children with PROS to evaluate for abnormalities in underlying organs including

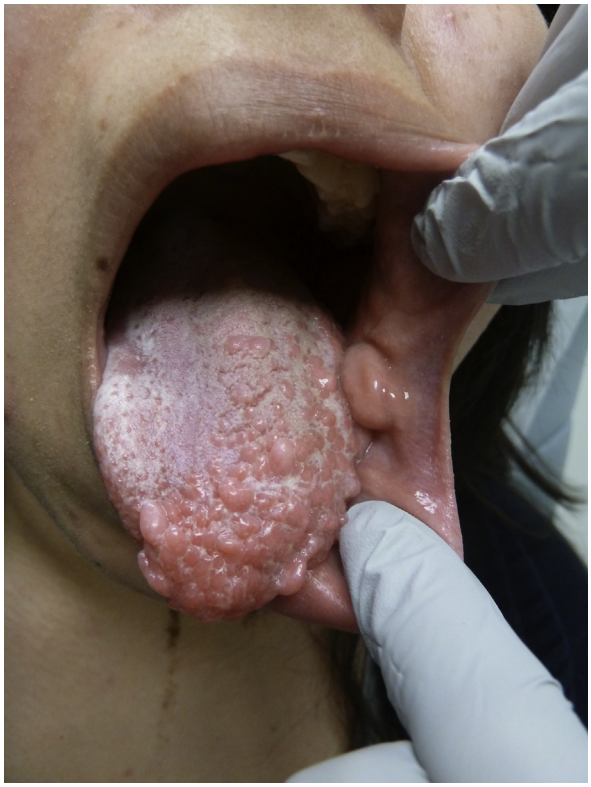

Fig 3. Hemi-tongue hypertrophy with mucosal neuromas of the tongue and buccal mucosa.

brain and spine and should be guided on the basis of the areas of involvement.[1] We report this case so that clinicians are aware of the potential for PROS disorders and the ability to confirm mutations in the tissues to allow for further characterization of these disorders.

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