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A Case of Simpson-Golabi-Behmel Syndrome Presenting with Cutaneous Findings

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Introduction

Simpson-Golabi-Behmel syndrome is a rare, X-linked recessive syndrome associated with mutations in the genes encoding glypicans 3 (GPC3) and GPC4. The majority of cases have been described in pediatric males, with those affected showing manifestations of overgrowth, congenital heart defects, and increased incidence of neoplasia. Due to the X-linked nature of this disorder, penetrance is not well understood in female cases. Very few cases of female presentations of Simpson-Golabi-Behmel syndrome have been described. We present a case of GPC3 gene mutation suggestive of Simpson-Golabi-Behmel syndrome in an adult female patient, diagnosed based on genetic testing performed due to a diagnosis of sebaceous carcinoma.

Patient Presentation

A 65 year old female with a past medical history of hypertension and hyperlipidemia originally presented to the dermatologist with a 0.5 cm erythematous, fleshy papule on her right lateral eyebrow that had been present for approximately 2 months. She reported that the lesion occasionally bled, but denied any associated systemic symptoms or other dermatological complaints at that time. The lesion was biopsied and diagnosed as a sebaceous carcinoma by dermatopathology. Due to known association correlation with genodermatoses, immunohistochemical staining of the biopsy specimen, a renal ultrasound and colonoscopy were ordered. IHC staining was negative for mismatch repair proteins associated with Lynch syndrome. The patient was diagnosed with low-grade papillary urothelial carcinoma. Due to intact expression of all four mismatch repair proteins associated with MTS, it was reassuring that the patient did not have Lynch syndrome. The Mayo Muir-Torre syndrome risk score was calculated with our patient receiving a score of 1 corresponding to a relatively low likelihood of having Muir-Torre/Lynch syndrome. Due to recent history of renal cancer, our patient elected to undergo genetic testing and was referred to a genetic counselor. Upon genetic investigation, our patient tested positive for a heterozygous mutation in the GPC3 gene c.595T>G (p.Arg199Gly). Germline mutations for MLH1, MSH2, MSH6, PMS2 and P20R were negative. Mutations in GFC3 are a well-established cause of Simpson-Golabi-Behmel syndrome (SGBS).

Results

SGBS is a rare, X-linked overgrowth/multiple congenital abnormality syndrome first reported by Simpson et al. in 1975.1 Thus far, only two genes have been implicated in the development of SGBS. The first and most well established gene causing SGBS encodes glypicans 3 (GPC3), a glycosyrophosphatidylinositol-linked cell surface heparan sulfate proteoglycan, which maps to Xp22.2 Similarly, GPC3 is located adjacent to GPC4 and belongs to a family of glypicans which encode heparan sulfate proteoglycan.2 GPC3 and GPC4 are believed to play a role in cell cell growth and division in embryonic mesodermal tissues, and may mediate insulin-like growth factor 2 (IGF2) action.2,3 Diagnosis guidelines have not yet been established, but previous cases are diagnosed based on suggestive findings in a patient with a hemizygous mutation involving GPC3 that may also involve GPC4.4 GPC3 expression has been linked with urothelial carcinomas, especially high grade tumors. Due to its X-linked nature, the majority of cases that have been discussed are in male patients. The majority of cases are also detected at an early age. The characteristics of SGBS include pre- and post-natal overgrowth, typical facies with prominent eyes and macroGLOSSIA, macropHACEO, organomegaly, other anomalies including diaphragmatic hernias, renal defects, gastrointestinal defects, skeletal anomalies and an increased risk of embryonal tumors, including Wilm tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma.5 To date, it is not known if other cancers are associated with mutation GPC.

Discussion

Female patients with SGBS males have been generally believed to be asymptomatic carriers, although there have been very few cases of female carriers with clinical expression of SGBS. In our review, eight cases of affected females were found described in the literature (Punnett 1994, Pilka et al 1996, Yano et al 2011, Mujezinovic et al 2016, Shimjojima et al 2016, Vaisfeld et al 2017, Schiwwani et al 2018). Explained possibilities for this phenomenon include random X-chromosome inactivation, which may promote phenotypic manifestations of SGBS in female carriers, and homozygosity/heterozygosity of the causal mutation.

References