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

Tessa Mullins, DO, PGY-3, Abigail Russell, DO, PGY-2, Chad Johnston, DO, FAAD | HCA LGHM Dermatology

Introduction

Simpson-Golabi-Behmel syndrome is a rare, X-linked recessive syndrome associated with mutations in the genes encoding glypican 3 (GPC3). 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 correlating with genodermatoses, immunohistochemical staining of the biopsy specimen, a renal ultrasound and colonoscopy were ordered. IHC staining was negative for any microsatellite instability for MSH-2, MSH-6, MLH-1 or PMS-2 and the patient’s colonoscopy was unremarkable. Complete renal ultrasound revealed mild prominence of the renal pelvis and infundibulum with no significant hydronephrosis. A follow up CT was performed of the abdomen and pelvis which showed of the abdomen and pelvis which showed (add in CT findings). The patient was diagnosed with low-grade papillary urothelial carcinoma. Due to recent history of renal cancer, our patient elected to undergo genetic testing and the patient was referred to a genetic counselor. Upon genetic investigation, our patient tested positive for a heterozygous mutation in the GPC3 gene c.595>T (p.Arg199*). Germline mutations for MLH1, MSH2, MSH6, PMS2 and PTEN were negative. Mutations in GPC3 are a well-established cause of Simpson-Golabi-Behmel syndrome (SGBS).

Discussion

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 glypican-3 protein (GPC3), a glycosylphosphatidylinositol-linked cell-surface heparan sulfate proteoglycan, which maps to Xp22.1.2 Similarly, GPC4 is located adjacent to GPC3 and belongs to a family of glypicans which encode heparan sulfate proteoglycans.3 4 GPC3 and GPC4 are believed to play a key role in cell growth and division in embryonic mesodermal tissues and may modulate insulin-like growth factor 2 (IGF2) action.2,3 Diagnosis guidelines have not yet been established, but previous cases described in the literature (Punnett 1994, Pilia et al. 1996, Yano et al. 2011, Schirwani et al. 2018) have attributed increased tumor risk with mild/moderate intellectual deficiency.1,6 SGBS is known to involve 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 correlating with genodermatoses, immunohistochemical staining of the biopsy specimen, a renal ultrasound and colonoscopy were ordered. IHC staining was negative for any microsatellite instability for MSH-2, MSH-6, MLH-1 or PMS-2 and the patient’s colonoscopy was unremarkable. Complete renal ultrasound revealed mild prominence of the renal pelvis and infundibulum with no significant hydronephrosis. A follow up CT was performed of the abdomen and pelvis which showed (add in CT findings). The patient was diagnosed with low-grade papillary urothelial carcinoma. Due to recent history of renal cancer, our patient elected to undergo genetic testing and the patient was referred to a genetic counselor. Upon genetic investigation, our patient tested positive for a heterozygous mutation in the GPC3 gene c.595>T (p.Arg199*). Germline mutations for MLH1, MSH2, MSH6, PMS2 and PTEN were negative. Mutations in GPC3 are a well-established cause of Simpson-Golabi-Behmel syndrome (SGBS).

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