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 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 associated correlation 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 of the right renal pelvis and subsequently underwent a right radical nephroureterectomy. Due to evidence of malignancy in her ureter with associated hematuria, a follow up cystoscopy was planned. Additional evidence of low-grade papillary carcinoma of the bladder was unfortunately found on cystoscopy. The patient was referred to a genetic counselor due to concern for possible Muir Torre syndrome.

Results

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 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 Xp26.[2] Similarly, *GPC4* is located adjacent to *GPC3* and belongs to a family of glypicans which encode heparan sulfate proteoglycans.[3] *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 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, macrocephaly, organomegaly, other anomalies including diaphragmatic hernias, renal defects, gastrointestinal defects, skeletal anomalies and an increased tumor risk with mild/moderate intellectual deficiency.[1,6] SGBS is known to be associated with an increased risk of embryonal tumors, including Wilms tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma.[7] To date, it is not known if other cancers are associated with mutation *GPC.*

Females that inherit the mutation of *GPC3* are 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, Pilia et al 1996, Yano et al 2011, Mujezinović et al 2016, Shimojima et al 2016, Vaisfeld et al 2017, Schirwani et al 2018).[8,2,6,9-11,3] Possible explanations for this phenomenon include random X-chromosome inactivation, which may promote phenotypic manifestations of SGBS in female carriers, and homozygosity/compound heterozygosity of the causal mutation.[11]

Discussion Continued

Penetrance of SGBS males is 100%, while in female carriers it is unknown.[7] The previous cases described were found in infant pediatric females due to concern for multiple congenital abnormality syndromes, either because of known SGBS within the family or concern for another congenital abnormality syndrome. In the first case presented by Punnett in 1994, the patient was initially diagnosed with Beckwith-Wiedemann syndrome, which was changed to SGBS after genetic testing revealed a balanced X;1 translocation at Xq25-27. Similarly, the case described by Pilia et al. was due to a balanced X;16 translocation. Yano described a female who was identified after her brothers were diagnosed with SGBS. Vaisfeld et al., Shimojima et al., Mujezinovic et al., and Schirwani et al. are later cases of females who have demonstrated significant features of SGBS as pediatric patients.[3] In general, mild physical findings of SGBS are seen in female carriers, such as increased stature, extranumerary nipples, coarse facies, abnormal hands, and midline defects.[7]

To the best of our knowledge, there have been no other cases of SGBS reported to date that have presented in an adult female with sebaceous carcinoma or with a clinical history of renal cancer. Challenges include accurate diagnosis of SGBS in a female because of its X-linked recessive inheritance, as well as lack of established criteria for diagnosis. Due to paucity of female cases described in the literature, multiple questions are raised. Is this syndrome more prevalent in females than previously recognized? Is there an association with other malignancies than previously described that may not be elucidated until later in life? This case points to a possible association of increased risk of cancers including sebaceous adenocarcinoma and renal cancer with carrier status of a mutated *G3PC* gene. While many questions remain unanswered, asking them highlights the importance of awareness of this syndrome and careful examination of those females found to be carriers.

References

1. Cottereau E, Mortemousque I, Moizard M-P, et al. Phenotypic spectrum of Simpson–Golabi–Behmel syndrome in a series of 42 cases with a mutation in GPC3 and review of the literature. *Am J Med Genet Part C Semin Med Genet.* 2013;163C:92–105.
2. Pilia G, Hughes-Benzie RM, Mackenzie A et al. Mutations in GPC3, a glypican gene, cause the Simpson-Golabi-Behmel syndrome. *Nat Genet.* 1996;12: 241–247.
3. Schirwani S, Novelli A, Digilio M, Bourn D, Wilson V, Roberts C, Dallapiccola B, Hobson E. Duplications of GPC3 and GPC4 genes in symptomatic female carriers of Simpson-Golabi-Behmel syndrome type 1. *Eur J Med Genet.* 2018. PubMed PMID: 30048822
4. Sajorda BJ, Gonzalez-Gandolfi CX, Hathaway ER, et al. Simpson-Golabi-Behmel Syndrome Type 1. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews.* Seattle, WA: University of Washington, Seattle; 2006. https://www.ncbi.nlm.nih.gov/books/NBK1219/
5. Aydin O, Yildiz L, Baris S, Dundar C, Karagoz F. Expression of Glypican 3 in low and high grade urothelial carcinomas. *Diagn Pathol.* 2015;10:34. https://doi:10.1186/s13000-015-0266-4
6. Yano S, Baskin B, Bagheri A, Watanabe Y, Moseley K, Nishimura A, Matsumoto N, Ray P. Familial Simpson–Golabi–Behmel syndrome: studies of X-chromosome inactivation and clinical phenotypes in two female individuals with *GPC3* mutations. *Clinical Genetics.* 2013;80:466-471. https://doi:10.1111/j.1399-0004.2010.01554.x
7. Tenorio J, Arias P, Martínez-Glez V, Santos F, García-Miñaur S, Nevado J, Lapunzina P. Simpson-Golabi-Behmel syndrome types I and II. *Orphanet J Rare Dis.* 2014;9:138. https://doi: 10.1186/s13023-014-0138-0.
8. Punnett HH. Simpson-Golabi-Behmel syndrome (SGBS) in a female with an X-autosome translocation. *Am J Med Genet.* 1994;50(4):391-393. https://doi:10.1002/ajmg.1320500424.
9. Mujezinović F, Krgovic D, Blatnik A, Zagradisnik B, Vipotnik T, Golec T, Tul N, Vokac N. Simpson-Golabi-Behmel syndrome: a prenatal diagnosis in a foetus with GPC3 and GPC4 gene microduplications. *Clin Genet.* 2016;90:99–101.
10. Shimojima K, Ondo Y, Nishi E, Mizuno S, Ito M, Ioi A, Shimizu M, Sato M, Inoue M, Okamoto N, Yamamoto T. Loss-of-function mutations and global rearrangements in GPC3 in patients with Simpson–Golabi–Behmel syndrome. *Hum Genome Var.* 2016;3:16033.
11. Vaisfeld A, Pomponi MG, Pietrobono R, Tabolacci E, Neri G. Simpson–Golabi–Behmel syndrome in a female: a case report and an unsolved issue. *Am J Med Genet.* 2017;173:285–8.

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