

Case Report

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

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Abstract

Description

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, and this case highlights that there may be an association between mutated *GPC3* carrier status and other cancers. 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.

Keywords

genetic diseases, X-linked; Simpson Golabi Behmel syndrome; gigantism; congenital, hereditary, and neonatal diseases and abnormalities; sebaceous carcinoma; Muir-Torre syndrome; heterozygous *GPC3* mutation; biopsy; neoplasms; sebaceous gland neoplasms

Introduction

Simpson-Golabi-Behmel syndrome is a rare, X-linked recessive syndrome associated with mutations in the genes encoding glypican 3 (*GPC3*).¹ 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, and this case highlights that there may be an association between mutated *GPC3* carrier status and other cancers. We present a case of *GPC3* gene mutation consistent with Simpson-Golabi-Behmel syndrome in an adult female patient.

Case Presentation

A 65-year-old female with a past medical history of hypertension and hyperlipidemia originally presented with a 0.5 cm fleshy papule on her

right lateral eyebrow that had been present for approximately 2 months. She denied any associated systemic symptoms or other dermatological complaints at that time. The lesion was biopsied and diagnosed as a sebaceous carcinoma. Immunohistochemical (IHC) 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 colonoscopy was unremarkable. A complete renal ultrasound revealed a mild prominence of the renal pelvis and infundibulum with no significant hydronephrosis. A computed tomography (CT) of the abdomen was performed, and 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. The cystoscopy found additional evidence of low-grade papillary carcinoma of the bladder. The patient was referred to a genetic counselor due to a con-

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cern for possible Muir Torre syndrome (MTS). Due to an intact expression of all 4 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 a recent history of renal cancer, our patient elected to undergo genetic testing. Our patient tested positive for a heterozygous mutation in the glypican-3 protein (*GPC3*) gene c.595>T (p.Arg199*). Germline mutations for *MLH-1*, *MSH-2*, *MSH-6*, *PMS-2* and *PTEN* were negative. Mutations in *GPC3* are a well-established cause of Simpson-Golabi-Behmel syndrome (SGBS) and pointed to the diagnosis of SGBS in our patient. The patient was counseled to continue regular follow-up with dermatology, oncology and urology.

Discussion

Simpson-Golabi-Behmel syndrome (SGBS) is a rare, X-linked overgrowth/multiple congenital abnormality syndrome first reported by Simpson et al. in 1975.¹ Only 2 genes have been implicated in the development of SGBS. The first and most well-established gene causing SGBS encodes *GPC3*, a glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycan, that 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 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.⁵

Due to its X-linked nature, the majority of cases that have been discussed are in male patients and 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 a mild/moderate intellectual deficiency.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 It is not known if other cancers are associated with mutations in *GPC3*.

Females that inherit the mutation of *GPC3* tend to be asymptomatic carriers. However, with random X-chromosome inactivation, individuals may have phenotypic manifestations of SGBS. There have been few female cases described in the literature.^{2,3,6,8-11} Penetrance of SGBS in female carriers is unknown. In the 8 reported female cases of SGBS in the literature, none have presented with sebaceous carcinoma or renal cancer. The previous cases described were found in infant females due to a concern for multiple congenital abnormality syndromes. 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 Xq25-27.⁸ Similarly, the case described by Pilia et al. was due to a balanced X;16 translocation.² Yano et al. described a female who was identified after her brothers were diagnosed with SGBS.⁶ Vaisfeld et al., Shimojima et al., Mujezinovic et al. and Schirwani et al. are later cases of infant females who have demonstrated significant features of SGBS.^{3,9-11}

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 an accurate diagnosis of SGBS in a female due to its X-linked recessive inheritance as well as a lack of established criteria for diagnosis. Due to the paucity of female cases described in the literature, multiple questions are raised. Is this syndrome more prevalent in females than previously recognized? Is there a greater 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 a 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.

Abbreviations

SGBS: Simpson-Golabi-Behmel Syndrome
GPC3: Glypican 3
GPC4: Glypican 4
IHC: Immunohistochemical
MSH-2: mutS homolog 2
MSH-6: mutS homolog 6
MLH-1: mutL homolog 1
PMS-2: PMS1 homolog 2
CT: Computed tomography
MTS: Muir-Torre Syndrome
PTEN: phosphatase and tensin homolog
IGF2: Insulin-like growth factor

Conflicts of Interest

The authors declare they have no conflicts of interest.

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