Case Report

A case of basal cell nevus syndrome with a *SUFU* mutation

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Abstract

Basal cell nevus syndrome (Gorlin syndrome) is a rare genetic condition characterized by multiple basal cell carcinomas, often arising before age 20.[1,2,3] Most cases result from a mutation in the patched 1 gene—part of the sonic hedgehog pathway. Rarely, this condition is related to a suppressor of fused gene mutation, which occurs downstream from Smoothened, and is unresponsive to Smoothened inhibitors including vismodegib and sonidegib. Notably, basal cell nevus syndrome, secondary to a suppressor of fused gene mutation, is associated with a higher incidence of childhood medulloblastoma with implications for the patient and offspring. A 72-year-old man with pearly papules coalescing into plaques across the nose and cheeks presented. The lesions had appeared as a teenager, and the patient reported his sister had similar lesions. Five biopsies, reviewed by three dermatopathologists, were consistent with basal cell carcinoma. Genetic testing was negative for patched 1 and patched 2 mutations but positive for a heterozygous suppressor of fused mutation. Patients with basal cell nevus syndrome should be treated with surgical excision, counseled on sun protection, screened and monitored for complications, and treated with vismodegib (if associated with patched 1 mutation) or itraconazole (if associated with suppressor of fused mutation).[3,5,6]

Introduction

Basal cell nevus syndrome (BCNS), known as nevoid basal cell carcinoma syndrome or Gorlin syndrome (GS), is a rare autosomal dominant inherited disorder caused by a mutation in the sonic hedgehog (SHH) signaling pathway.[1-3] The inheritance has greater than a 90% penetrance, but mostly a variable expression of traits.[3] The gene most associated with this syndrome is the patched 1 (*PCTH1*) gene but is rarely associated with the suppressor of fused (*SUFU*) and patched 2 (*PCTH2*) mutations.[2, 3] The classical presentation of this syndrome is multiple basal cell carcinomas, developmental anomalies, odontogenic keratocysts of the jaw, palmar and plantar pitting, and an increased risk of medulloblastoma development in childhood.[2-4] Notably, there are few key differences in disease presentation between those with the more common *PCTH1* mutation and the rarer *SUFU* mutation.[4] Medications such as vismodegib target the SHH pathway but are not effective in the treatment of the downstream *SUFU* mutation. We report a unique case of BCNS caused by a *SUFU* mutation with basal cell carcinoma lesions localized to only the facial region.

Case Synopsis

A 72-year-old man with a past medical history significant for chronic obstructive pulmonary disease and hypersensitivity lung disease presented with enlarging facial papules that had developed as a teenager. The patient denied any personal or family history of cancer but reported that his sister had similar lesions involving her face. Physical examination findings included multiple pearly papules coalescing into plaques across the nose and bilateral cheeks, mild frontal bossing, a few small scattered palmar pits, and multiple milia-like cysts on the face (Figure 1). Five separate shave biopsies were taken

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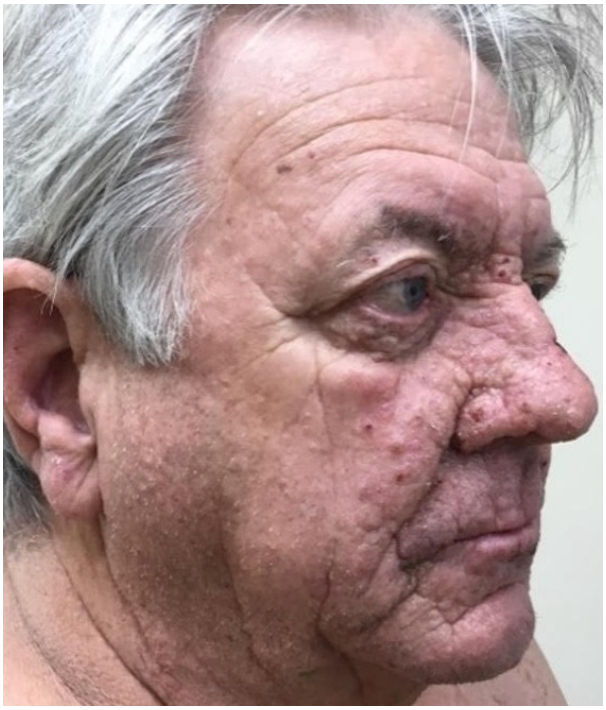


Figure 1. *Mild frontal bossing, multiple pearly papules coalescing into plaques across the nose and bilateral cheeks, few milia-like cysts, several small, scattered pits on the palms.*

from the pearly papules and plaques. Three separate dermatopathologists reviewed each biopsy and agreed that the results were consistent with four nodular basal cell carcinomas and one infundibulocystic basal cell carcinoma (Figure 2A-B). Genetic testing was procured on the patient owing to a clinical suspicion of BCNS and was found to be negative for *PTCH1* and *PTCH2* mutations and positive for a heterozygous *SUFU* mutation (Figure 3). The patient then underwent radiographic imaging of the mandible and chest to evaluate for cyst of the jaw and bifid or splayed ribs. Imaging was found to be negative for these findings. Once a diagnosis of BCNS was made, the patient was referred to Mohs surgery for removal of BCCs on the face and to primary care to rule out medulloblastoma. He was also referred for genetic counseling.

Discussion

Basal cell nevus syndrome, or Gorlin syndrome, can be seen in young children but typically presents by 20 to 25 years of age.[4-6] It is an autosomal dominantly inherited disease typically caused by a mutation of the *PCTH1* gene, which is associated with the SHH pathway.[2-4] Less commonly, this disease relates to a mutation in the *SUFU* gene.[2-4] The SHH pathway is responsible for managing cell proliferation and differentiation. Importantly, this pathway is regulated and inhibited at multiple points to minimize unregulated tumor growth. Activating mutations along the SHH pathway can lead to numerous growths and malignancies. In the SHH pathway, *PTCH* inhibits *Smoothened* (*Smo*) and represses unregulated

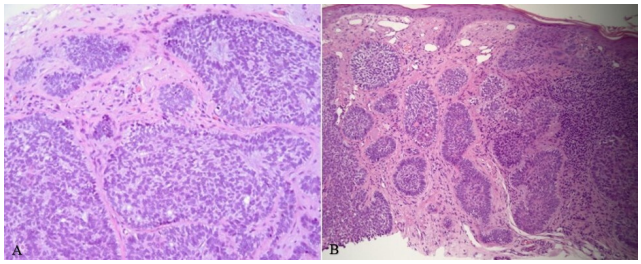
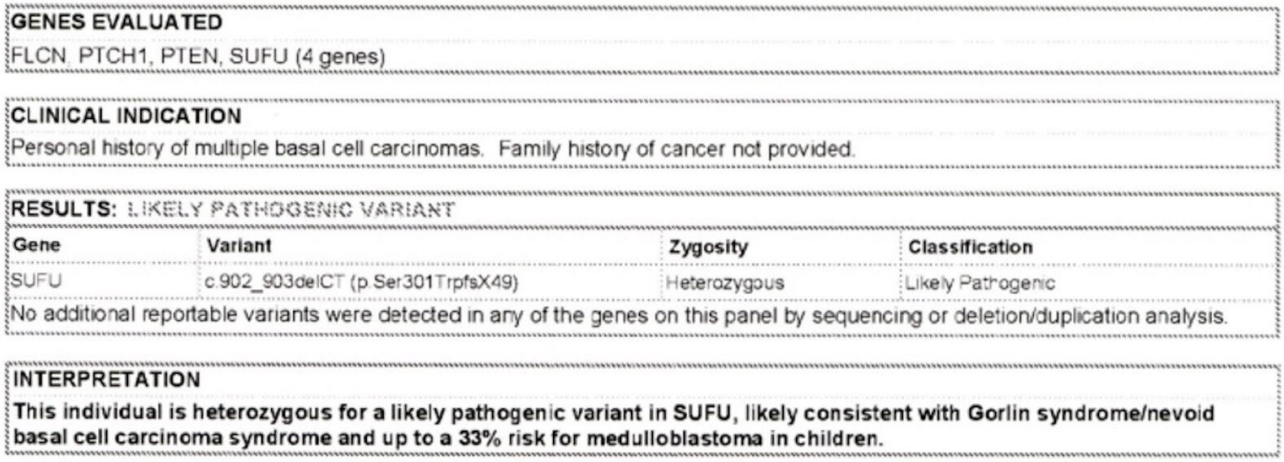


Figure 2. ***A)*** *Dermal nodular basaloid aggregates with large atypical hyperchromatic nuclei and peripheral palisading (hematoxylin and eosin, x20).* ***B)*** *Dermal nodular aggregates of atypical basaloid cells with peripheral palisading and inflammation in a fibromyxoid stroma and focal areas of retraction (hematoxylin and eosin, x10).*

growth. When an activating ligand binds *PTCH*, the repression on *Smo* is relieved and phosphorylation of *Smo* causes binding of *Smo* and *SUFU*, resulting in downstream nuclear translocation of Gli and continued gene transcription. *SUFU* is one of the suppressors along this pathway to ensure appropriate growth management and signaling. Over the years there have been a few proposed diagnostic criteria for BCNS, but the most notable diagnostic criteria for BCNS were described by Evans et al in 1993.[7] The manuscript suggested that BCNS could be diagnosed if two major or one minor criterion or if two minor criteria are present. The major criteria included more than two BCCs or one BCC in a patient under 20 years of age; three or more palmar pits, odontogenic keratocysts, falx cerebri calcifications; or a first degree relative with the disease.[7] The minor criteria that were described include bifid or splayed ribs or fused vertebrae, frontal bossing, medulloblastoma, ovarian or cardiac fibroma, cyst of the lymphomesenteric system, or a congenital malformation (ie, cleft lip, polydactyly, or eye anomaly).[7] These criteria have been modified by others but have all included a similar consensus as described.[1] Our patient had more than two BCCs, palmar pitting, a first degree relative with a similar disease, mild frontal bossing, and a confirmed *SUFU* mutation confirming the diagnosis of basal cell nevus syndrome. Our patient's presentation is unique in that this patient's BCCs were localized to the face and this was a late onset case of BCNS. As such, there have only been a few case reports of patients with BCNS with only facial localization of BCCs and with a later onset as seen in our patient (Table 1).[8,9]

In basal cell nevus syndrome, it is important to make a distinction between the more common *PCTH1* mutation and the rarer *SUFU* mutation (Table 2). A few studies have highlighted this difference and the important clinical implications. Ogden et al noted that there is a 33% risk of medulloblastoma in those with the *SUFU* mutation versus a less than 2% risk in the *PCTH1* mutation.[4] This increased risk, especially seen in childhood, might lead to further complications including cutaneous tumors if the medulloblastoma was irradiated as a form of treatment and warrants increased surveillance in youth.[4] Other differences have been found including decreased incidence



GENES EVALUATED

FLCN, PTCH1, PTEN, SUFU (4 genes)

CLINICAL INDICATION

Personal history of multiple basal cell carcinomas. Family history of cancer not provided.

RESULTS: LIKELY PATHOGENIC VARIANT

Gene	Variant	Zygosity	Classification
SUFU	c.902_903delCT (p.Ser301TrpfsX49)	Heterozygous	Likely Pathogenic

No additional reportable variants were detected in any of the genes on this panel by sequencing or deletion/duplication analysis.

INTERPRETATION

This individual is heterozygous for a likely pathogenic variant in SUFU, likely consistent with Gorlin syndrome/nevoid basal cell carcinoma syndrome and up to a 33% risk for medulloblastoma in children.

Figure 3. *Genetic test findings: document showing results of genetic testing positive for heterozygous SUFU mutation. Note: PTCH1 gene evaluation included PTCH2, which was found to be negative.*

Table 1. *Comparison of Late-Onset Basal Cell Nevus Syndrome (BCNS) Features From Case Reports and Our Patient Presentation.*

Feature	Kim CS, Na YC[8]	Hasan Ali O, Yurchenko AA, Pavlova O, et al[9]	Our Patient
Age of Onset	40-year-old male with BCCs developing since adolescence	Brothers developed first BCCs after age 40	72-year-old male with BCCs developing since adolescence
Clinical Features	Black pigmented macules on the face, jaw cysts, bifid ribs, and falx cerebri calcification	Late-onset BCCs after age 40 with palmar pitting and additional somatic mutations	Pearly papules on face, mild frontal bossing, small palmar pits, milia-like cysts
BCCs	Multiple facial BCCs, biopsied lesions	Late-onset facial BCCs	Multiple BCCs localized to the face (nose and cheeks)
Tumor Histology	Not specified	Not specified	Nodular and infundibulocystic BCCs, consistent with BCNS
Genetic Findings	Patient declined genetic testing	Germinal splice site mutation in *PTCH1* with loss of heterozygosity in BCCs	Positive for heterozygous *SUFU* mutation, negative for *PTCH1* and *PTCH2*
Family History	Not specified	Two brothers with similar late-onset BCCs	Family history of similar facial lesions in sister
Radiographic Findings	Positive for odontogenic cyst, bifid left sixth rib, and calcifications of the falx cerebri	Positive for odontogenic cysts	Negative for odontogenic cysts, bifid ribs, or other skeletal abnormalities
Follow-up and Outcome	Symptom-free 10 months post-surgery	Follow-up not specified but indicates hypomorphic nature of *PTCH1* mutation	Referred for Mohs surgery, genetic counseling, and surveillance for medulloblastoma

of keratocysts of the jaw, as well as increased incidence of ovarian fibromas in patients with the *SUFU* mutation.[4] Interestingly, our patient did not have a history of medulloblastoma nor was he found to have any keratocysts in his jaw.

Another notable difference in the *SUFU* and *PCTH1* mutations with Gorlin syndrome is the treatment therapies available including vismodegib.[4] Vismodegib is an inhibitor that targets *Smo*, which in turn blocks the SHH pathway.[3,4] This inhibitor has been found to slow the rate of BCC development and aid in the reduction of BCC burden especially in those with multiple basal cell carcinoma that are refractory to local excision.[3] Unfortunately, vismodegib does not target the *SUFU* mutation as it is further down the SHH pathway.[4] This poses further difficulties for those with the *SUFU* mutation. Itraconazole, however, has been shown in some cases to block the SHH pathway in the event of a *SUFU* and *PCTH1* mutations, but this mechanism is poorly understood and poses other drug interaction risks.[4] There have been reports of patients achieving clinical regression of BCC with anti-PD-1 inhibitors in the event of failure of a SHH in-

Table 2. *Comparison of the Presentation of Basal Cell Nevus Syndrome (BCNS) in Patients with* PTCH1 *and* SUFU *Mutations.*

Feature	*PTCH1* Mutation	*SUFU* Mutation
Incidence of BCNS	More common (majority of BCNS cases)	Rare (accounts for a smaller subset of BCNS)
Tumor Presentation	Frequent basal cell carcinomas (BCCs), often early in life	Fewer BCCs compared to *PTCH1* mutation, but still significant
Other Neoplasms	Increased risk of other cancers (eg, medulloblastoma, ovarian fibromas)	Risk of medulloblastomas and other CNS tumors, but less frequent overall
Cystic Lesions	Common occurrence of jaw cysts (odontogenic keratocysts)	Rare or less prominent occurrence of jaw cysts
Early Onset of Disease	Typically presents in childhood with multiple skin lesions	Skin manifestations generally appear later, in the fourth to sixth decades of life
Skin Features	Multiple BCCs, palmar/plantar pits, and other characteristic skin findings	Skin findings can be less pronounced, but BCCs still present
Neurological Involvement	Rare, but can have medulloblastoma or other CNS involvement	Increased risk of medulloblastoma, especially in younger patients
Genetic Testing/ Diagnosis	Mutation in *PTCH1* gene (more widely studied and recognized)	Mutation in *SUFU* gene (rarer and less well understood)

hibitor.[10] This could be a potential treatment option for patients with a *SUFU* mutation. Other options include topical 5-flurouracil or imiquimod as adjunctive or primary treatment depending on the clinical case.[3]

Management of BCNS includes a multistep and multidisciplinary approach. Basal cell carcinomas can be removed by local excision or Mohs surgery if indicated.[3, 4] Vismodegib or itraconazole can be used for diffuse or refractory BCC or those who have a contraindication to surgical excision.[3,4] If BCNS is suspected, it is important to evaluate genetic mutations in all cases, especially considering the variable yet important differences as discussed.[4,7] Genetic counseling should be sought for patients and their family members in order for them to better understand the disease.[4] Close monitoring for the development of medulloblastoma in those with the *SUFU* mutation is appropriate because of the increased risk.[3, 4] In all cases, patients should be counseled on appropriate sun protective measures and to avoid ionizing radiation from diagnostic testing, if possible, to help reduce the risk of further cancer.[3,4]

Conclusion

Basal cell nevus syndrome or Gorlin syndrome is a rare but important disease to keep in mind in any patient with multiple basal cell carcinomas or young individuals with a BCC. If BCNS is suspected, genetic testing should be obtained for *PTCH1*, *PTCH2*, and the *SUFU* mutation owing to the different monitoring and treatment implications. In any case, a multidisciplinary approach should guide the patient's journey for the best possible outcome.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Agrawal A, Murari A, Vutukuri S, Singh A. Gorlin-goltz syndrome: Case report of a rare hereditary disorder. *Case Rep Dent*. 2012;2012:475439. doi:10.1155/2012/475439. PMID:23050170

2. Colegio O, O'Toole E, Pontén F, Lundeberg J, Asplund A. In: Bolognia J, Schaffer J, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier Limited; 2018:1870.

3. Barankin B, Lam J. Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome). In: Stern R, Robinson J, eds. *UpToDate*. UpToDate; 2022.

4. Ogden T, Higgins S, Elbaum D, Wysong A. The relevance of a suppressor of fused (SUFU) mutation in the diagnosis and treatment of Gorlin syndrome. *JAAD Case Rep*. 2018;4(2):196-199. doi:10.1016/j.jdcr.2017.10.011. PMID:29892665

5. Huq AJ, Walsh M, Rajagopalan B, et al. Mutations in SUFU and PTCH1 genes may cause different cutaneous cancer predisposition syndromes: Similar, but not the same. *Fam Cancer*. 2018;17(4):601-606. doi:10.1007/s10689-018-0073-7. PMID:29356994

6. Fernández LT, Ocampo-Garza SS, Elizondo-Riojas G, Ocampo-Candiani J. Basal cell nevus syndrome: An update on clinical findings. *Int J Dermatol*. 2022;61(9):1047-1055. PMID:34494262

7. Evans DG, Ladusans EJ, Rimmer S, et al. Complications of the naevoid basal cell carcinoma syndrome: Results of a population-based study. *J Med Genet*. 1993;30(6):460-464. doi:10.1136/jmg.30.6.460. PMID:8326488

8. Kim CS, Na YC. Basal cell nevus syndrome with excessive basal cell carcinomas. *Arch Craniofac Surg*. 2021;22(2):122-125. doi:10.7181/acfs.2021.00136. PMID:33957740

9. Hasan Ali O, Yurchenko AA, Pavlova O, et al. Genomic profiling of late-onset basal cell carcinomas from two brothers with Nevoid basal cell carcinoma syndrome. *J Eur Acad Dermatol Venereol*. 2021;35(2):396-402. doi:10.1111/jdv.16767. PMID:32564428

10. Ligtenberg KG, Hu JK, Damsky W, et al. Neoadjuvant anti-programmed cell death 1 therapy for locally advanced basal cell carcinoma in treatment-naive patients: A case series. *JAAD Case Rep*. 2020;6(7):628-633. doi:10.1016/j.jdcr.2020.05.010. PMID:32613057