The relevance of a suppressor of fused (SUFU) mutation in the diagnosis and treatment of Gorlin syndrome

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INTRODUCTION

Nevoid basal cell carcinoma syndrome, also known as *Gorlin syndrome* (GS), is an aberrant activation of the sonic hedgehog pathway (Hh). GS was first described in the literature in 1894 and the Hh pathway's role in its development was discovered thereafter.[1] The Hh pathway regulates cell growth and development of the integumentary, central nervous, and musculoskeletal systems, where its overactivation causes abnormalities. In GS, this manifests as, among other clinical sequela, numerous basal cell carcinomas (BCC) that vary in quantity from a few to several thousand. BCC as a symptom of GS occurs in 90% of white patients but only 40% of African-American patients because of increased epidermal melanin in the latter group and thus increased protection from ultraviolet light exposure.[2] Onset of these BCCs can occur as young as 3 years; however, they typically begin to appear at approximately 25 years of age.[1] The additional clinical sequelae of GS are included in the criteria for diagnosis, established in 1993 by Evans et al[3] and revised in 1997 by Kimonis.[4] These include keratocysts of the jaw, palmar, and plantar pitting; bilamellar falx cerebri calcification; and splayed, bifid, or fused ribs.[1]

In GS, the Hh pathway mutation is most often of the gene patched 1 (*PTCH1*), which encodes a transmembrane receptor found early in the pathway. In rare cases, a mutation in the suppressor of fused (*SUFU*) gene, encoding a component downstream of *PTCH1*, can cause GS (Fig 1). It was not until 2009 that an *SUFU* mutation was implicated in GS with its relevance centered on a clinically distinct phenotype including a 33% risk of medulloblastoma development compared with a less than 2% chance with a *PTCH1* mutation.[5,6] The treatment of these medulloblastomas in infants by craniospinal

Abbreviations used:

BCC:	basal cell carcinoma
GS:	Gorlin syndrome
Hh:	Hedgehog pathway
PTCH1:	patched 1
SMO:	smoothened
SUFU:	suppressor of fused

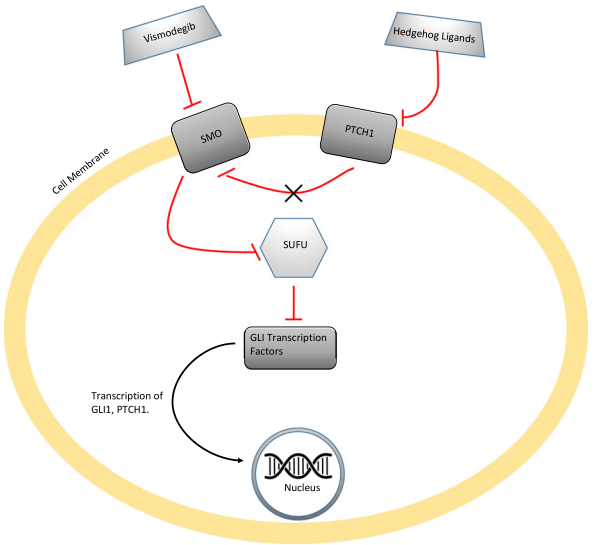

Fig 1. Diagram of the normal Hh pathway. Upon binding to Hh ligands, *PTCH1* releases SMO. The activation of SMO disallows *SUFU* from inhibiting GLI transcription factors. The overactivation of GLI transcription factors promotes uncontrolled cell growth and cancer.[12]

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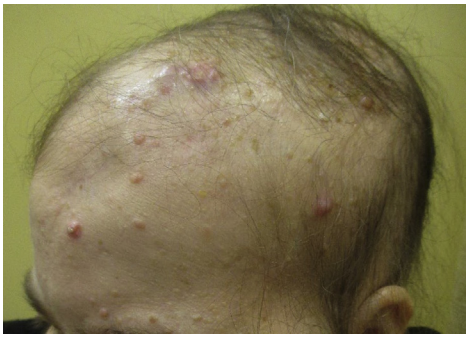

Fig 2. Numerous pink papules on the scalp and upper forehead with occasionally prominent and characteristic rolled borders. Biopsies were positive for BCC. Also note the sparse hair density.

irradiation therapy may significantly affect the onset, number, and aggressiveness of GS associated BCCs and lead to future development of meningiomas, which have the potential to induce epileptic activity in 40% to 50% of cases.[2,6,7] Thus, alternative therapeutic considerations, such as surgical resection coupled with postoperative chemotherapy, may be warranted in these patients. Here, we present the case of a 37-year-old woman found to have GS with a confirmed *SUFU* mutation. She had a history of medulloblastoma at 10 months old treated with craniospinal irradiation with consequent development of meningioma at age 35 and more than 100 BCCs by the time of presentation.

CASE REPORT

The patient was referred to the University of Southern California's high-risk skin cancer clinic with a history of more than 100 BCCs on her scalp and on the posterior aspect of her neck. At 10 months old, she had a medulloblastoma diagnosed, for which she received irradiation therapy to the head, neck, and partial spine. Additional medical history included hydrocephalus, cognitive deficits, leiomyosarcoma of ovaries, seizure disorder, and meningioma. She had a family history positive for various malignant and benign tumors including esophageal cancer, leiomyosarcoma, and meningioma. Seven of her 10 aunts and uncles and her maternal grandmother suffered from medulloblastomas. Upon presentation, the patient was noted to have palmar pitting, macrocephaly with frontal bossing and moon facies, numerous papules on her face and neck that began 10 years prior, and sparse hair density on the scalp (Fig 2). Multiple papules biopsied from the forehead and brow were found to be positive for trichoepitheliomas (Fig 3). Several from the scalp region were positive for BCC, in addition to the history of more than 100 BCCs diagnosed over the course of her lifetime within the field of prior radiation therapy. At this time, a differential diagnosis comprising Bazex syndrome, Rombo syndrome, Brooke-Spiegler syndrome, and GS was developed. Given the patient's personal and family history in addition to the clinical presentation, GS topped the list of differential diagnoses, and the patient was accordingly referred for genetic testing. Upon genetic testing, the patient was confirmed to have GS by way of a monoallelic *SUFU* mutation. The mutation, *SUFU* c.597+dupG, was noted to disrupt the splice donor site on the exon of the *SUFU* gene and act as a pathogenic variant.

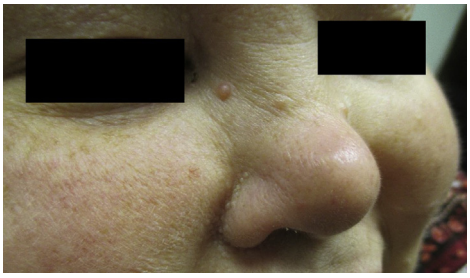

Fig 3. Multiple skin-colored translucent papules were noted on the nose and along the nasolabial folds. Biopsy results were positive for trichoepitheliomas. Also of note is the patient's moon facies.

DISCUSSION

Key differences in the presentation of GS as a result of *SUFU* versus *PTCH1* mutations are presented in Table I.[8] Prominent among these is the increased incidence of medulloblastoma in patients with *SUFU* mutation.[6] Medulloblastomas typically develop in GS patients between 21 and 28 months of age, however, may develop sooner as seen in our patient. Treatment with craniospinal irradiation may lead to a variety of deficits and increased numbers of cutaneous tumors later in life. A study that analyzed the outcomes of 23 patients of median age 2.6 years with medulloblastomas treated first with postoperative chemotherapy then with irradiation therapy upon disease progression found that all radiated patients lost cognitive function at a rate of 3.9 intelligence quotient points per year, all had sensory decline and all became dependent on hormone replacement therapies.[9] Secondary tumors, mainly meningioma and increased BCCs in Gorlin patients, are also linked to craniospinal irradiation. Thus, our patient's cognitive deficit, high quantity of BCCs, and meningioma with subsequent seizure disorder may all be connected to early irradiation therapy. This finding elucidates the need for unique treatment considerations in *SUFU* patients that weigh the

Table I. Criteria for GS diagnosis

	SUFU (~5% of all GS patients)	PTCH1 (50-90% of all GS patients)
Major criteria (% of GS patients)		
Multiple BCCs: greater than 2 or 1 before age 20 (67%-77%)	~80% by 50 y	~80% by 50 y
Odontogenic keratocysts of jaw (proven on histology) (63.2%)	~0% (0/11 reported patients)	~62%
Three or more palmar or plantar pits (55.6%)	~36% (4/11 reported patients)	Common (no numbers reported)
Bilamellar calcification of falx cerebri (64.3%)	~91% (10/11 reported patients)	Common (no numbers reported)
Bifid, fused or splayed ribs	Not specified in literature	Not specified in literature
First-degree relative with GS (47.1%)	Not specified in literature	Not specified in literature
Minor criteria:		
Childhood medulloblastoma	~33%	<2%
Macrocephaly (66.7%)	Clinically less pronounced ~100% (2/2 reported cases)	Clinically more pronounced ~40% (2/5 reported cases)
Radiologic abnormalities: bridging of the sella turcica, vertebral anomalies, fusion or elongation of vertebral bodies, modelling defects or flame-shaped lucencies of the hands and feet	Not specified in literature	Not specified in literature
Congenital malformations: cleft lip or palate, frontal bossing, course face, hypertelorism	Not specified in literature	Not specified in literature
Skeletal deformities including: sprengel deformity, pectus deformity, syndactyly of digits	~56% (5/9 reported patients)	Not specified in literature
Ovarian fibromas	~50% (3/6 reported patients)	~7% (4/61 reported patients)

These criteria were modified in 1997 by Kimonis from criteria previously established by Evans et al in 1993. Patients that meet 2 major criteria or 1 major criterion and 2 minor criteria fulfill diagnostic requirements for GS.[2,5,6,8]

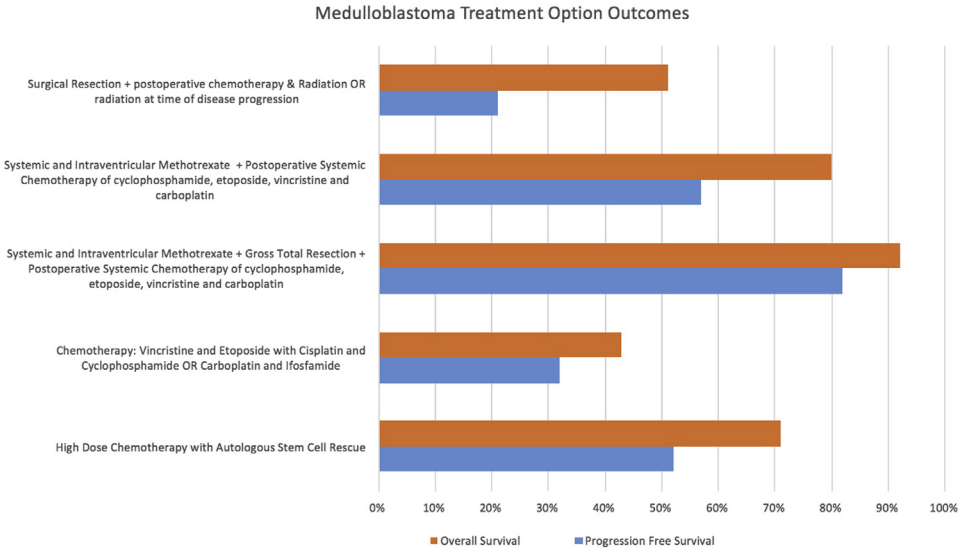

Fig 4. The various treatment options for medulloblastomas and their associated survival rates.[10]

long-term risks of irradiation therapy with its benefits.[10] In cases in which radiation therapy is deemed the best therapeutic option, the dose should be minimized by combining with other treatment modalities (Fig 4). Thus, the diagnosis of *SUFU*-associated GS not only begets increased surveillance for

medulloblastomas in youth, but also unique treatment considerations once they are diagnosed. *SUFU*-associated GS also deems the use of vismodegib, a targeted smoothened (SMO) inhibitor, virtually useless. Vismodegib is commonly used for *PTCH1*-associated GS, however, has not been shown to be effective against BCCs from *SUFU* mutation, as *SUFU* is located downstream of the drug's target, SMO.[10] Itraconazole can effectively block the Hh pathway in the case of both types of mutations and inhibit cell proliferation; however, its pathway is poorly understood and it cannot be used in patients taking antiepileptic medications.[11] Had our patient not suffered from epilepsy that necessitated antiepileptics, itraconazole, one of the few therapies found to be effective in controlling *SUFU*-related BCCs, may have been used. Given the disparate presentations and treatment regimens appropriate for Gorlin patients with distinct mutations, the importance of recognizing the syndrome and its underlying genetic mutations becomes clear. Thus, patients should undergo genetic testing in all cases. In those with *SUFU*-associated GS, there should be heightened surveillance for the development of medulloblastoma. In those with a standing diagnosis of medulloblastoma, a risk benefit analysis is indicated to determine the long-term utility of radiation or alternative therapies.

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