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Case Report

The First Case of SUFU Related Gorlin Syndrome Presenting with Infantile Medulloblastoma in Hong Kong

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Abstract Gorlin syndrome (GS) is a rare, clinically and genetically heterogeneous autosomal dominant disorder primarily characterised by early onset of odontogenic keratocysts, multiple basal cell carcinomas and palmar or plantar pits. Two genetic mutations, namely PTCH1 and SUFU, have been described to be the culprit of such syndrome. PTCH1 and SUFU, as the two groups of GS, have different underlying mechanism and clinical presentation. In particular, the *SUFU* gene mutation is associated with higher risk of developing infantile medulloblastoma and jaw cysts. However, individuals presenting with an infantile medulloblastoma are mostly presumed to be sporadic. Here we have reported the first case of SUFU related Gorlin syndrome presenting with infantile medulloblastoma in Hong Kong. The clinical phenotype and underlying mechanism have also been discussed.

Key words *Gorlin syndrome; Infantile medulloblastoma; SUFU*

Introduction

Medulloblastoma is one of the major causes of morbidity and mortality in paediatric oncology. Historically, classification of medulloblastoma is based on immunohistochemistry. Recent technological advancement in molecular testing redefined the classification into four groups, namely wingless (Wnt), sonic hedgehog (Shh), Group 3 and Group 4.[1] Different subgroups of medulloblastoma have difference in clinical presentation, age of onset and recurrence pattern. In particular, recent testing revealed the *SUFU* gene, together with the *PTCH1* gene, are strongly associated with the sonic hedgehog pathway, and subsequently Gorlin syndrome (GS) with the presentation of early onset of medulloblastoma. This article reports a case of Gorlin syndrome first presenting with infantile medulloblastoma. Diagnosing Gorlin syndrome is important as the patient are highly susceptible to basal cell carcinoma, congenital skeletal abnormalities and other tumourigeneses.

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Case Report

The proband is now a 20-year-old gentleman. He was the first child of the family born at full term with birth weight of 3.52 kg. His perinatal history was unremarkable, except he experienced frequent repeated vomiting from 1 month of age. His head circumference was increased from 50th to 90th percentile at 5 months of age. Imaging at the same age showed tumour at the posterior cranial fossa. He had underwent subtotal excision at 1 year old with histology confirmed to be medulloblastoma in year 2000. However, no histological subclassification was performed at that time. He was put on postoperative standard risk medulloblastoma Baby POG Chemotherapy protocol. The chemotherapy regime included Vincristine, Cisplatin and Cyclophosphamide. But parents refused postoperative

radiotherapy. He was in complete remission afterwards. On subsequent follow up, he was noted to have features of Gorlin syndrome such as macrocephaly and dermal pits on palmar and plantar region (Figure 1). He was then referred to the Clinical Genetic Service for assessment.

Genetic Testing shows that he has maternal inherited heterozygous pathogenic splice site variant c.684-1G>A in *SUFU* gene (NM_016169.3), therefore substantiated the molecular diagnosis of SUFU related Gorlin syndrome. After surgical intervention, he has mild residual cerebellar deficit with no intellectual disability. There was no dental, skeletal and skin cancer on follow up. And there is no family history of cancer.

Discussion

Medulloblastoma

Recently, an international consensus was reached for the molecular subgrouping of paediatric medulloblastomas, which has different genetic causes and therefore different recurrence and metastasis.[2] The four groups include wingless (Wnt), sonic hedgehog (Shh), Group 3 and Group 4. It was found that Wnt tumours are very likely to have an onset between 6-12 years old, while Shh tumours age of onset ranges from infant to adult.[3] The Hedgehog pathway is responsible for embryonic and fetal development. The product of the PTCH gene is a transmembrane receptor for sonic hedgehog.[4] Once the sonic hedgehog binds to PTCH, the intracellular signal transducer SMO will be activated, initiating the downstream signaling events, including GLI1 and SUFU. SUFU is a negative regulator of the Hedgehog signaling pathway.[5] Mutation of *PTCH1* gene and *SUFU* gene result in unregulated activation of hedgehog pathway, predisposing to unregulated cell proliferation and apoptosis inhibition. The genetic mutation of Shh group is very similar to that in Gorlin syndrome, which explains why Gorlin syndrome is highly associated with medulloblastoma. It was also found that the Shh subgroup are more likely to experience local recurrence while group 3 and group 4 are prone to metastatic recurrence.[6] For the Shh tumours, historically PTeCH1 has been identified as the gene that is causative for medulloblastoma in Gorlin syndrome. It was until 2009 that SUFU, another component of the Shh pathway, was found to be associated with a family of clinically diagnosed Gorlin syndrome with childhood onset of medulloblastoma.[7] Such association established genetic heterogeneity of Gorlin syndrome, and increased the chance of molecular diagnosis of Gorlin syndrome.

Medulloblastoma are mostly presumed to be sporadic. Recent research indicates genetic mutations play an important role in causing these rare brain tumours.[8] In particular, the molecular subgroup 1 (Wnt) and subgroup 2 (Shh) are highly associated with oncogenes such as *TP53, PTCH1, SUFU, BRCA2* and *PALB2*.[8] It was also observed that patients of the Shh subgroup have a high prevalence of damaging germline mutation. Yet, less than half of these patients are suspected to have such mutations based on medical records, leading to delayed or missed diagnosis of cancer predisposing genes and syndromic disorders.[8] It is therefore strongly advised that regular genetic counselling and screening shall be provided to these group of patients.

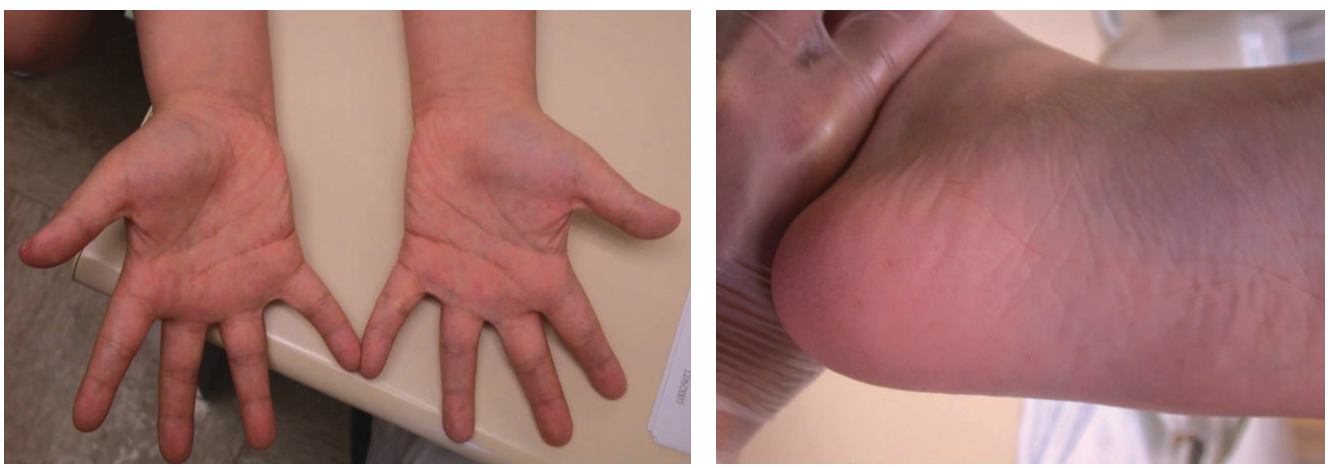

Figure 1 Dermal palmar and plantar skin pits.

Gorlin Syndrome

Gorlin syndrome, also called Nevoid Basal Cell Carcinoma syndrome (NBCCS), is an autosomal dominant disorder that leads to skeletal developmental abnormalities and multi-systemic tumourigenesis.[1] The frequency of this disorder ranges from 1/30827 in the UK to 1/238500 in Japan.[9,10] Around 1% of patients with Gorlin syndrome develop medulloblastoma usually at the age of 2 to 3 years,[9] while basal cell carcinoma and other tumours tend to have age of onset in adolescent or adult.[11] Lifelong observation and careful medical attention shall be provided to patients with Gorlin syndrome to monitor the progression of tumours.

First modern literature documented this syndrome was by human geneticist Gorlin in 1960s.[12] Basal cell carcinoma, skeletal abnormalities and odontogenic keratocysts (jaw cysts) were the three major findings in his study.[12] With recent technological advancement of medical apparatus, pathological skeletal deformation and detection of tumourigenesis can be identified with CT and MRI scans, while molecular diagnosis can be made with specific arrays and Whole Exome Sequencing. Gorlin syndrome can involve congenital abnormalities of multiple systems, while dermatological and skeletal manifestations are reported more often.[13] The major criteria for diagnosing Gorlin syndrome includes: (1) Multiple (>2) basal cell carcinomas or one under 30 years, or >10 basal cell naevi. (2) Any odontogenic keratocyst (proven on histology), or polyostotic bone cyst. (3) Palmar or plantar pits (3 or more). (4) Ectopic calcification: lamellar or early (<20 years) falx calcification. (5) Family history of NBCCS. In 1992, the location of gene for Gorlin syndrome is first identified. It was found that the microdeletion of 9q22.3, which includes deletion of PTCH1, is the causative gene of GS.[14] In 2002, *SUFU* mutation is newly identified as a cause of medulloblastoma, which is a loss of function of the tumour suppressor gene. In 2009, a causative link between *SUFU* mutation and GS through a case report of *PTCH1*-negative GS family. Current genetic testing for GS include Next Generation Sequencing and Whole Exome Sequencing which covers both *PTCH1* and *SUFU* gene.

In 2017, a publication in the BMJ described the genotype phenotype relationship of Gorlin syndrome.[15] Some of the key findings, together with findings from other publications, are tabulated in Table 1.

In retrospect, this patient was presented similarly as the newly-discovered molecular subtype *SUFU* gene mutation, with higher incidence of childhood medulloblastoma and absence of jaw cysts. The exceptions are that some of the classical presentation of Gorlin syndrome, i.e. macrocephaly and dermal pits on plantar region.

It is important to differentiate PTCH1 and SUFU subgroup of Gorlin syndrome as they have different clinical presentation, recurrence rate and treatment options. The message from this *SUFU* mutated proband is that *SUFU* type Gorlin syndrome cause higher incidence and unusual early onset of childhood medulloblastoma. What is more alarming is that *SUFU* type patients have a higher life risk to develop meningioma or an ovarian fibroma, therefore clinicians are advised to keep a close monitoring of tumour progresses. Moreover, in the Sonic Hedgehog pathway, the G-protein coupled receptor SMO is the key molecule for inhibition. Scientists have discovered SMO-specific targeted drugs such as vismodegib and sonidegib, which has been approved by the FDA for treatment of Basal Cell Carcinoma. Yet, this drug cannot be used on SUFU type Gorlin syndrome. Thus, drugs targeting other signaling molecules like Gli-1, PI3K-mTOR and PKC are under clinical trial. Clinicians should pay attention to the development of the new targeted therapy and which subtypes they are addressed to respectively.

Table 1

	***PTCH1* gene mutation**	***SUFU* gene mutation**
Pathway	Sonic Hedgehog	Sonic Hedgehog
Rate of medulloblastoma / meningioma	Lower	Higher
Histopathology of medulloblastoma[16]	Classical	desmoplastic/MBEN
Jaw cysts	No	Multiple
Risk of Basal Cell Carcinoma in carriers[17]	Higher	Lower
Treatment of SMO inhibition	Susceptible	Resistant

Conclusion

Gorlin syndrome is a multi-systemic disease that is susceptible to tumourigenesis which require lifelong and careful medical attention from a multidisciplinary team. Infantile and childhood medulloblastoma at the age of onset below six are associated with Gorlin syndrome, while medulloblastoma within the age 6-12 are more likely to be sporadic. It should come to pediatricians' attention that children with early onset of brain tumours could have underlying genetic cause, thus appropriate genetic testing shall be done during or after the course of surgical or medical treatment.

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Declaration of Interest

None

References

1. Fujii K, Miyashita T. Gorlin syndrome (nevoid basal cell carcinoma syndrome): update and literature review. Pediatrics International 2014;56:667-74.
2. Millard NE, De Braganca KC. Medulloblastoma. J Child Neurol 2016;31:1341-53.
3. Ellison DW, Dalton J, Kocak M, et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol 2011;121:381-96.
4. Smith MJ, Beetz C, Williams SG, et al. Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. J Clin Oncol 2014;32:4155-61.
5. Kieran MW. Targeted treatment for sonic hedgehog-dependent medulloblastoma. Neuro-oncology 2014;16:1037-47.
6. Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ, Schüller U. Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol 2013;14;1200-7.
7. Pastorino L, Ghiorzo P, Nasti S, et al. Identification of a SUFU germline mutation in a family with Gorlin syndrome. Am J Med Genet A 2009;149:1539-43.
8. Waszak SM, Northcott PA, Buchhalter I, et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol 2018;19:785-98.
9. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM. Birth incidence and prevalence of tumor-prone syndromes: Estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327-32.
10. Endo M, Fujii K, Sugita K, Saito K, Kohno Y, Miyashita T. Nationwide survey of nevoid basal cell carcinoma syndrome in Japan revealing the low incidence of basal cell carcinoma. Am J Med Genet A 2012;158A:351-7.
11. Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 1997;69:299-308.
12. Gorlin RJ, Vickers RA, Kellin E, Williamson JJ . The multiple basal cell nevi syndrome. An analysis of a syndrome consisting of multiple basal cell carcinoma, jaw cysts, skeletal anomalies, medulloblastoma and hyporesponsiveness to parathormone. Cancer 1965;18:89.
13. Muzio LL. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Orphanet J Rare Dis 2008;3:32.
14. Muller E II, Hudgins L. 9q22.3 Microdeletion [updated 2014 Feb 20]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Mirzaa GM, Amemiya A, editors. GeneReviews? [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. PMID: 21850767.
15. Evans DG, Oudit D, Smith MJ, et al. First evidence of genotype-phenotype correlations in Gorlin syndrome. J Med Genet 2017;4: 530-6.
16. Slade I, Murray A, Hanks S, et al. Heterogeneity of familial medulloblastoma and contribution of germline PTCH1 and SUFU mutations to sporadic medulloblastoma. Fam Cancer 2011;10:337-42.
17. Brugieres L, Remenieras A, Pierron G, et al. High frequency of germline SUFU mutations in children with desmoplastic/nodular medulloblastoma younger than 3 years of age. J Clin Oncol 2012; 30:2087-93.