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Gorlin Syndrome and Desmoplastic Medulloblastoma: Report of 3 Cases With Unfavorable Clinical Course and Novel Mutations

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Abstract

We present three cases of genetically confirmed Gorlin syndrome with desmoplastic medulloblastoma (DMB) in whom tumor recurred despite standard therapy. One patient was found to have a novel germline missense *PTCH1* mutation. Molecular analysis of recurrent tumor using fluorescent in situ hybridization (FISH) revealed *PTEN* and/or *PTCH1* loss in 2 patients. Whole exome sequencing (WES) of tumor in one patient revealed loss of heterozygosity of *PTCH1* and a mutation of *GNAS* gene in its non-coding 3' -untranslated region (UTR) with corresponding decreased protein expression. While one patient died despite high-dose chemotherapy (HDC) plus stem cell rescue (ASCR) and palliative radiotherapy, two patients are currently alive for 18+ and 120+ months respectively following retrieval therapy that did not include irradiation. Infants with DMB and GS should be treated aggressively with chemotherapy at diagnosis to prevent relapse

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but radiotherapy should be avoided. The use of molecular prognostic markers for DMB should be routinely used to identify the subset of tumors that might have an aggressive course.

Keywords

clinical features; Gorlin syndrome; medulloblastoma; mutation; PTCH; whole genome sequencing

INTRODUCTION

Gorlin- Lentz Syndrome (GS) is an autosomal dominant genetic disorder characterized by multiple basal cell carcinomas, odontogenic keratocysts, hyperkeratosis of palms, and soles, skeletal abnormalities, intracranial ectopic calcifications, facial dysmorphism, and intellectual disability.[1] GS is caused by mutations in the *PTCH 1* gene with complete penetrance and a variable phenotype.[1] About 3–5% of these children develop DMB during infancy.[2] Outcome for patients with GS and DMB is mostly favorable following conventional therapy although the current consensus is that radiotherapy should be avoided in these young children to prevent exacerbation of neuro-cognitive deficits and proclivity to develop secondary malignancies.[3,4] Herein, we report on three children with DMB and GS, one of whom has a novel *PTCH1* mutation. While all of them suffered disease recurrence despite intensive therapy, two are currently alive without disease following salvage therapy that did not include irradiation.

CASE REPORTS

Patient No. 1

A 2 year-old white female presented with a posterior fossa mass (Fig. 1A). She also had developmental delay, gait problems, frontal bossing, and a bifid right third rib. She underwent gross total resection (GTR) of the posterior fossa mass (Fig. 1B). Pathology revealed DMB. Genetic analysis revealed a germline nonsense mutation of *PTCH 1* (C>T, exon 18), confirming GS. She was initially treated with standard chemotherapy only.[5] She suffered a local relapse in the superior vermis 18 months following diagnosis (Fig. 1C). Salvage treatment included GTR followed by induction chemotherapy (IC) with four cycles of dose intensive cyclophosphamide (2 g/m²/day for 2 days every 4 weeks with granulocyte colony stimulating factor support) followed by high-dose chemotherapy ([HDC]; Carboplatin [either 500 mg/m² or a dose based on Calvert's formula to achieve an area under the curve concentration of 7 mg/ml per minute, whichever was less] on days –8, –7, and –6, followed by thiotepa 300 mg/m² and etoposide 250 mg/m² daily on days –5, –4, and on –3) + autologous stem cell rescue (ASCR) day 0 as described previously in a report from our institution[6] and no radiotherapy. The patient is now 120+ months post-HDC with no evidence of disease recurrence.

Patient No. 2

A 1.8-year-old male presented with developmental delay and gait impairment. His mother was diagnosed with GS as an adult based on odontogenic keratocyst and palmar pitting. Neuroimaging of the child revealed hydrocephalus and a tumor in superior cerebellar vermis

that was extending into the pineal recess (Fig. 1D). He initially underwent a third ventriculostomy and biopsy that confirmed DMB. Genetic testing revealed an inherited germline *PTCH1* mutation (G>A, exon 12 at the splice donor site of intron 13) confirming GS. He underwent IC and HDC + ASCR similar to Patient No. 1 after achieving minimal residual disease (Fig. 1E). However he developed metastatic disease 6 months following HDC (Fig. 1F) and subsequently died of disease despite palliative radiotherapy.

Patient No. 3

A 2.5-year old female presented with frontal bossing, macrocephaly, synorthis, and bifid third rib. MRI revealed a right cerebellar mass (Fig. 1G) after she reported severe headaches and sporadic vomiting. She underwent GTR of tumor (Fig. 1H) and pathology revealed medulloblastoma with extensive nodularity. Genetic analysis revealed a spontaneous novel missense mutation on exon 12 (c 1670 C>G) of *PTCH 1* at the cDNA level and p. Thr557Arg at the protein level. Post-operatively, patient received IC and HDC + ASCR without radiotherapy (same myeloablative chemotherapy regimen as Patient No. 1). Twelve months following HDC, she suffered a local relapse in the right cerebellar hemisphere (Fig. 1I). She was enrolled on a phase II study of oral GDC0449 (Vismodegib™, Genentech Corporation, San Francisco, CA) a Smoothened inhibitor, for children with recurrent medulloblastoma, received 150 mg orally q daily for 28 days, had a partial response following 2 cycles, but suffered progressive disease after the 4th cycle.[7] She underwent surgical resection of tumor after enrollment on a phase I immunotherapy study (reMATCH protocol).[8] She completed treatment successfully and remains disease-free 18+ months following completion of vaccine treatment.

METHODS

Genomic DNA from peripheral blood mononuclear cells was PCR-amplified for analysis of exon 1–23 of the *PTCH* gene and their flanking splice sites. Bi-directional sequence was obtained and DNA sequence was analyzed and compared to the published gene sequence. The result was confirmed in a new DNA preparation by repeat sequence analysis. Array-based comparative genomic hybridization (a-CGH) was also performed. The array contains DNA oligonucleotide probes that cover all coding exons of the *PTCH* gene. Hybridization data was analyzed using Genomic workbench v5 software (Agilent Technologies, Santa Clara, CA) to evaluate copy number at the exon level for deletions and duplications. Immunohistochemical (IHC) studies, FISH, and WES were performed as previously described.[9–12]

RESULTS

Pathology and Molecular Studies

Microscopic examination of tumor obtained in Patient No. 1 showed an embryonal neoplasm characterized by cells with scant cytoplasm and round to slightly elongated nuclei. Widespread nodules within the tumor exhibited a reduced cell density and neurocytic differentiation. Areas of extensive nodularity with streaming of neurocytic cells were seen. No anaplastic features were present. The Ki-67 labeling index was approximately 30%.

FISH assay of tumor tissue obtained at relapse was performed to assess copy number status at *MYC*, *MYCN*, *PTCH1*, and *PTEN* loci. The tumor exhibited deletion of *PTCH1* against a partial polysomy as well as hemizygous deletion of *PTEN* but no significant abnormalities of the *MYC* or *MYCN* genes. Additional sequencing could not be performed due to depletion of tumor tissue.

Microscopic examination of tumor at diagnosis from Patient No. 2 showed an embryonal neoplasm consistent with DMB. Molecular analysis of tumor was not performed due to lack of available tissue.

Microscopic examination of tumor at diagnosis from Patient No. 3 showed medulloblastoma with extensive nodularity. Intercellular desmoplasia in internodular regions was confirmed by reticulin staining. Intra nodular tumor cells expressed synaptophysin. The tumor was placed in the SHH subgroup by IHC.[11] FISH analysis to evaluate copy number alterations in tumor obtained at second relapse did not show any abnormalities in *PTEN*, *MYC*, or *MYCN* loci but did reveal homozygous loss of *PTCH1*. WES was performed on frozen tumor tissue obtained following relapse on GDC-0449 along with matched germline DNA and revealed a *PTCH1* mutation in normal tissue carried over into the tumor with an additional frame shift mutation constituting a “double hit” (Supplementary Table S1).[13] Interestingly, mutation in the non-coding 3' UTR region of the *GNAS* gene was found in tumor tissue but not in germline DNA (Supplementary Table S1). Immunohistochemistry of tumor tissue using *GNAS* antibody (sc-823, Santa Cruz, CA) revealed decreased Gs protein α subunit ($G\alpha_s$) expression as compared to normal cerebellum (Fig. 2A and B). Additional non-recurrent mutations were found including *TEC*, *TMED1*, and *SLTRK3* but none in the *Smoothed* (*SMO*) gene.

DISCUSSION

GS is a rare condition occurring in 1 in 56,000 individuals.[2] About 3–5% of patients with GS develop cerebellar DMB usually within the first 2 years of life.[2] The syndrome is either due to de novo (60% of cases) or inherited germline *PTCH 1* mutations.[14] *PTCH* is a human analog of the *Drosophila* segment polarity gene and consists of 23 exons spanning 50 kB encoding a 1447 amino acid, 12-pass transmembrane glycoprotein.[14] Paracrine signaling from Sonic Hedgehog (SHH) secreted by Purkinje cells of the cerebellum or constitutional activation of *PTCH1* due to mutation, results in dissociation of the serpentine G-protein coupled receptor SMO from PTCH, which then translocates into the tip of the primary cilium and releases GLI2 from its natural repressor, SUFU. GLI2 then migrates into the nucleus and transcriptionally activates genes involved in cellular proliferation of granule cell precursors (GCP) of the cerebellum leading to tumor formation.[15] Over 70% are nonsense mutations and occur predominantly in the larger external loops of the protein. Missense (17%) and putative splice mutations (10%) account for the rest.[14,16] The novel missense mutation on exon 12 (c 1670 C>G) at the cDNA level and p. Thr557Arg at the protein level in patient No. 3 has not been previously reported in GS or as a polymorphism in normal individuals. This mutation is at a highly conserved site within the *PTCH 1* gene and is likely to interfere with normal function. Furthermore, pathogenicity of this mutation was validated by the “second-hit” frame shift mutation at the same locus (L85fs) in the

patient's tumor. GS should be considered in all infants who present with DMB and confirmed by genetic testing to enable proper genetic and treatment counseling of parents. [17,18]

Disease recurrence in our patients suggests that outcome in GS and DMB is not uniformly favorable as previously reported.[3] The reasons for treatment failure in these patients are unclear. Recent WES including methylation studies of SHH medulloblastoma tumors have unleashed a wealth of information regarding specific molecular alterations that provide more accurate predictions of clinical outcome following standard therapy as compared to clinical staging alone.[19–21] Recent studies have shown that *GLI2* amplification, chromosome 14 loss, 10q deletion (resulting in loss of *PTEN*, as was seen in Patient No. 1), *MYCN* amplification, anaplasia, and/or metastatic disease at diagnosis as conferring the worst prognosis for patients with SHH medulloblastoma.[20,22] The presence of a mutation in the 3' –UTR of the *GNAS* gene in the relapsed tumor tissue (post GDC0449) of Patient No. 3 along with decreased $G\alpha_s$ expression is intriguing. He et al., have recently described that this heterodimeric G protein functions as a tumor suppressor and molecular switch transmitting various G protein coupled receptor signals.[12] Low or absent protein expression was found in a subset of patients with aggressive SHH medulloblastoma. [12] It is therefore possible low $G\alpha_s$ expression could have contributed to tumor relapse in this patient although we have not been able to assess protein expression in her previous tumor. Given that the *PTCH1* mutation is one of the specific biomarkers for predicting response to a Smoothed inhibitor,[21] we anticipated that this patient would benefit from GDC0449. The short-lived response to the drug suggested acquired drug resistance. However, her tumor did not reveal the specific point mutation of *SMO* (D473H) known to cause resistance to GDC0449.[23,24] While multiple approaches have been used in recent years to treat infant DMB and avoid radiotherapy (using intrathecal methotrexate, HDC + ASCR),[25] The prolonged remission in Patient No. 1 following HDC (using carboplatin + etoposide + thiotepa) + ASCR alone would encourage us to recommend this approach in all infants in DMB and GS at diagnosis to improve outcome. It is possible now to identify a subset of patients with aggressive disease by performing IHC and FISH for specific markers of poor prognosis including *PTEN* and *GNAS* and should be done in all patients for accurate estimation of prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Axial T-1 weighted image with gadolinium shows a large enhancing mass arising from the vermis in case 1 (A), following GTR (B), and local recurrence 18 months following HDC (C). Sagittal T-1 weighted image with gadolinium shows a large enhancing mass in the superior vermis extending up into the pineal region in case 2 (D), following subtotal resection (E), and axial T-1 weighted image following gadolinium showing metastatic relapse (F) measuring 1.12 cm in the right cerebellum 6 months following HDC. Axial T-1 weighted image with gadolinium showing a large enhancing mass in the right cerebellar hemisphere at diagnosis (G), following GTR (H), and local relapse (I) 12 months following HDC.

Fig. 2. Immunohistochemical staining of G α_s protein using anti-mouse antibody normal cerebellum of a 13 year old female and tumor tissue from Patient No. 3 demonstrating normal expression (brown) in normal cerebellum (A) and decreased expression in tumor cells (B). Hematoxylin/eosin counterstaining.