TARGETED TREATMENT FOR SHH+ MEDULLOBLASTOMA IN A PEDIATRIC PATIENT WITH GORLIN SYNDROME

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INTRODUCTION

- Gorlin Syndrome - Most cases caused by a pathogenic variant of PTCH1, which plays a role in the Sonic Hedgehog (SHH) signaling pathway.
- Affected patients have developmental anomalies, multiple basal cell carcinomas, and an increased risk of developing a medulloblastoma in early childhood.
- **Figure 1:** Clinical Manifestations of Gorlin Syndrome

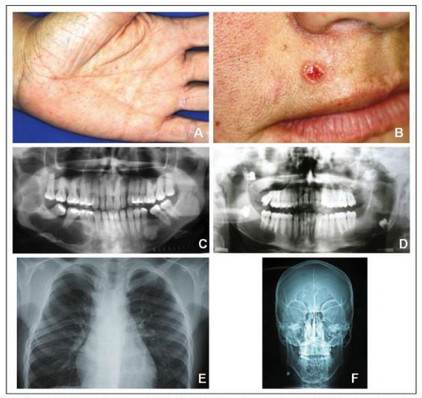
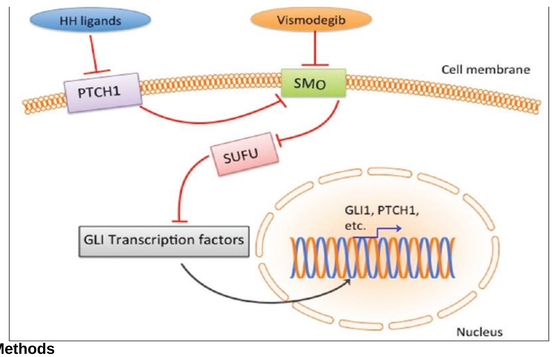


Fig. 1: Some of clinical manifestations of NBCCS. **A.** Multiple palmar pits (patient 13). **B.** Basal cell carcinoma ocated in fluff region (patient 13). **C.** One KCOT located in ramus and posterior mandible and with multilocular pattern (patient 4). **D.** Presence of four synchronous KCOT with unilocular pattern involving 3rd impacted molar (patient 11). **E.** Chest radiograph demonstrating bifid ribs (patient 12). **F.** Antero-posterior skull radiograph showing calcification of the falx cerebri (patient 2).

- Mainstay treatment of MB consists of a combined-modality approach utilizing RT, but this is not recommended in patients with Gorlin Syndrome patient due to the increased risk of developing basal cell carcinomas.
- Vismodegib is an SHH signaling pathway inhibitor recently FDA approved for treating the basal cell carcinomas in Gorlin Syndrome. This case study discusses the use of Vismodegib as a targeted therapy for SHH+ medulloblastoma (MB).
- **Figure 2:** Vismodegib's role in SHH pathway

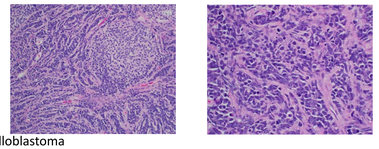


Methods

- A chart review was performed for this single case study.

PATIENT PRESENTATION

- 4-year-old Hispanic female
  - Past Medical History: macrocephaly, large birth weight, missing right pupil and lens w/ associated blindness, developmental delay
- Presentation:
  - Worsening ataxia, beginning Nov. 2015
- Imaging:
  - Posterior fossa tumor (Figure 6) with intracranial and intraspinal metastases
- **Figure 3:** Pathology of posterior fossa tumor



  - Medulloblastoma
  - Nodular/desmoplastic morphology with large cell/anaplastic changes
  - Molecular profile: SHH+/p53-/MYCN-
- Genetic Testing
  - Positive PTCH1 gene mutation, consistent with diagnosis of Gorlin Syndrome
- Initial therapy
  - 5 cycles of chemo per COG ACNS1221
  - Avoid radiation therapy due to increased risk of developing basal cell carcinomas

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- Recurrent widespread metastatic disease
  - Begin radiation now, as benefit outweighs risk.
  - Post RT → no evidence of residual disease

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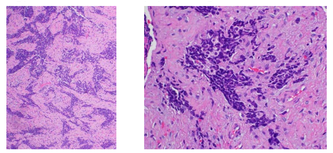
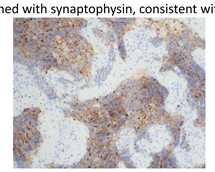
- Evidence of recurrent, metastatic, extraneural SHH+ MB
  - PET scan positive at left mandible & left pelvis
  - MRI of mandibular tumor (Figure 7)
  - **Figure 4:** Pathology of left mandible biopsy showing infiltrative small cell malignancy



  - **Figure 5:** Biopsy stained with synaptophysin, consistent with metastatic medulloblastoma



- Patient approved to begin Vismodegib
  - Not currently FDA approved to treat MB, but is being studied in clinical trials
  - Initially beneficial, but patient's tumor was far too advanced and continued to progress
  - Currently being treated by palliative care for pain management

IMAGING

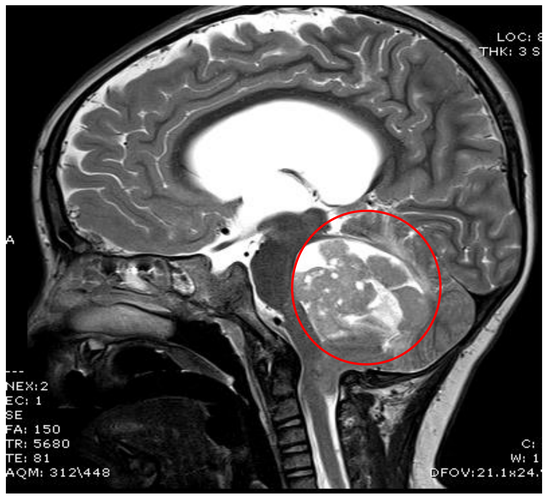


Figure 6: Nov 2015 - Original posterior fossa tumor

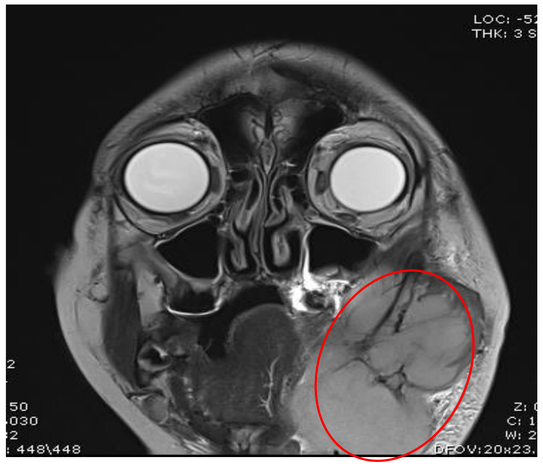


Figure 7: Feb 2019 - Mandibular recurrence of tumor

CONCLUSION

- Mainstay treatment of MB consists of a combined-modality approach utilizing RT, but that is risky in patients with Gorlin syndrome.
- The use of Vismodegib as targeted therapy in our patient was initially promising, but the tumor still progressed.
- We present this case to raise awareness to the potential complications of treating MB in those with Gorlin syndrome and to discuss the possible benefit of Vismodegib for these patients.
- Multi-institutional studies are required to determine whether the drug should be included in a comprehensive treatment plan for patients with Gorlin syndrome and SHH+ MB.

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