A Case of Gorlin Syndrome With Rare Late Presentation of First Basal Cell Carcinoma

Renata Brindise, DO, PGY-4

Oakwood Southshore Medical Center
Disclosure

I have no actual or potential conflict of interest in relation to this program/presentation.
What’s In A Name?

- Nevoid Basal Cell Carcinoma Syndrome
- Gorlin-Goltz Syndrome
- Gorlin Syndrome

- Rare disorder characterized by tumorigenesis and developmental defects
- First described by Gorlin and Goltz in 1960
An Interesting Case...

- 39 year old Caucasian male with a non-healing lesion on the bridge of nose
- Present for several weeks and was stable in size
- Lesion spontaneously bled and was painful
- ROS was grossly negative
History

- Several oral surgeries in adolescence for complications related to odontogenic keratocysts
- Palmar and plantar pitting present since childhood
- An unclassified rib deformity
- Family history was unremarkable
Examination

- 3 mm dome shaped papule located on the left nasal bridge
- Notable frontal bossing
- Palmoplantar pitting
Management and Follow-Up

- Shave biopsy was performed on the lesion in question
- Biopsy revealed an ulcerated basal cell carcinoma (BCC), nodular type
- Development of four additional BCCs within 15 months time
- Treated with MOHS microscopic surgery
- Continued follow-up every three months
Gorlin Syndrome: Introduction

- Rare multi-system disorder involving the formation of multiple basal cell carcinomas and various other neoplasms
- Development of various skeletal, dermatologic, and visceral abnormalities
- Prevalence is estimated to be 1:50,000 to 1:250,000 in the general population
- Male/female ratio is 1:1
Gorlin Syndrome: Introduction

- Occurs in all ethnic groups
- Most commonly occurs in Caucasians
- Autosomal dominant with variable penetrance and expressivity
- Up to 40% of cases may be sporadic as a result of germline mutations
- Average age of diagnosis is 13 years
- Average age for detection of BCC’s is 20 years

Gorlin Sydrome: Genetic Aspects

- Abnormalities in the long arm of chromosome 9 (q22.3-q31)
- Loss or mutation of PTCH1 (patched homologue 1), a tumor suppressor gene part of the Hedgehog signaling pathway
- PTCH involved in carcinogenesis, organogenesis, and odontogenesis
- Mutations in PTCH2 (Patched2), SMO (Smoothened), and SHH (Sonic Hedgehog) may also play a role
Gorlin Syndrome: Clinicopathologic Aspects

- Anomalies described:
  - Skeletal
  - Skin
  - Craniofacial
  - Sexual
  - Neurologic
  - Ophthalmic
  - Orofacial
Gorlin Syndrome: Clinicopathologic Aspects

- Multiple BCC’s
- Odontogenic keratocysts or polyostotic bone cysts
- Palmoplantar pitting
- Milia
- Calcification of the falx cerebri
- Bifid ribs or fused vertebrae
- Frontal bossing
- Large occipital frontal circumference
- Cardiac or ovarian fibromas
- Medulloblastomas
- Lymphomesenteric cysts
- High arched palate
- Cleft lip/palate
- Polydactyly/syndactyly
- Strabismus
- hypertelorism


Gorlin Syndrome: Diagnostic Criteria

- **Major criteria:**
  - More than 2 BCC’s, or one in patients younger than 30 years of age
  - Any odontogenic keratocyst or polyostotic bone cyst
  - Three or more palmar or plantar pits
  - Lamellar or early falx cerebri calcification in patients younger than 20 years of age
  - A positive family history of Gorlin syndrome

- **Minor criteria:**
  - Congenital skeletal anomalies
  - Occipital-frontal circumference greater than the 97th percentile with frontal bossing
  - Cardiac or ovarian fibromas
  - Medulloblastoma
  - Lymphomesenteric cysts
  - Congenital malformations such as cleft lip/palate, polydactylism or eye anomalies including cataract, colobomas, or microphthalmus

Gorlin Syndrome: Management of BCC’s

- Excisional or Mohs surgical removal
- CO2 lasers, phototheraphy, curettage, electrodessication, cryosurgery
- Topical imiquimod, topical 5-fluorouracil, and intralesional IFN alpha 2b

Leger M et al. Nevoid basal cell carcinoma syndrome. Dermatology online journal 2011 (1087-2108), 17 (10), 23.
Gorlin Syndrome: Vismodegib

- Hedgehog signaling pathway inhibitor approved for the treatment of locally advanced and metastatic basal cell carcinomas
- Tang et al. published a randomized, double-blind, placebo controlled study on 42 patients with Gorlin Syndrome
  - Patients were followed for a mean of 8 months, primary endpoint being reduction in the incidence of new basal cell carcinomas that were eligible for surgical resection with vismodegib versus placebo
  - Reduced the mean rate of new, surgically eligible basal-cell carcinomas per year as compared with placebo (2 vs. 29 cases per group per year, P<0.001)
  - As a secondary endpoint, reduction in size (longest diameter) was evaluated in existing clinically significant basal cell carcinomas (-65% vs. -11%, P= 0.003)
  - Vismodegib treated patients also had less resections of BCC lesions as compared to placebo (0.31 surgeries per patient vs. 4.4 for placebo, P<0.001)
  - FDA approved dosing is 150mg by mouth daily until disease progression or unacceptable adverse effects are experienced
  - Most common adverse effects: muscle spasms, alopecia, dysgeusia, weight loss, fatigue, and nausea
What’s new on the horizon?

- Topical SMO inhibitor in clinical trials (LD225)
- Has been evaluated in eight Gorlin patients
- Patients were treated twice daily for four weeks with 0.75% LDE225 and vehicle
- 27 total BCCs were treated, 13 with LDE225 and 14 with vehicle
- 13 lesions treated with topical LDE 225 and evaluated macroscopically and dermatoscopically
  - Complete clinical response in three lesions
  - Partial response in nine lesions
  - One with no clinical response
- LDE225 cream and the vehicle were tolerated well with no skin toxicities
- No significant abnormalities in physical examination, vital signs, electrocardiographs, blood work, or urinalysis results were noted
- May be a promising alternative for patients who are unable to tolerate the side effect profile of an oral SMO inhibitor
- Oral itraconazole also currently being studied as a hedgehog pathway inhibitor

In summary…

- Presented an unusual case of Gorlin syndrome with late presentation of first basal cell carcinoma
- Due to the prevalence of the syndrome, it is likely that many dermatologists will be faced with the cutaneous management of a Gorlin syndrome patient during their time in practice
- Many promising and novel treatments continuously in development for the management of widespread, locally advanced, or metastatic basal cell carcinomas
Thank You

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References