Treatment of Multiple Unresectable Basal Cell Carcinomas from Gorlin-Goltz Syndrome: A Case Report

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Abstract. *Background: Nevoid basal cell carcinoma syndrome (NBCCS), which is also known by other names, including Gorlin-Goltz syndrome and multiple basal-cell carcinoma (BCC) syndrome, is a rare multi-systemic disease inherited in a dominant autosomal manner with complete penetrance and variable expressivity. The main clinical manifestations include multiple BCCs, odontogenic keratocysts of the jaw, hyperkeratosis of the palms and soles, skeletal abnormalities, intracranial calcifications and facial deformities. Patients and Methods: A 31-year-old male diagnosed with Gorlin-Goltz syndrome with multiple unresectable facial BCCs was treated with the Hedgehog inhibitor vismodegib. Results: After one month of therapy on vismodegib, there were significant reductions in the size of multiple BCCs on the patient's face. The patient remains on this therapy. Conclusion: Hedgehog pathway inhibition is an effective strategy to treat unresectable BCCs from Gorlin-Goltz syndrome. Although vismodegib shows some promising clinical results in the early phase of its use, there are concerns of possible resistance developing within months. Duration of therapy, role of maintenance treatment and drug modification to reduce resistance need to be explored in future case studies.*

Nevoid basal cell carcinoma syndrome (NBCCS), which is also known by other names, such as Gorlin-Goltz syndrome, multiple basal-cell carcinoma syndrome and multiple basalioma syndrome, is a rare multisystemic disease inherited in a dominant autosomal manner with complete penetrance and variable expressivity (1-3). The name NBCCS was proposed by professors Gorlin and Goltz in 1960 (1). The incidence of the syndrome is 1/57,000 to 1/256,000 with no predilection to sex (4, 5).

The pathogenesis of NBCCS is attributed to abnormalities linked to the long arm of chromosome 9 (q22.3-q31) (4). This abnormality results in mutations in human patched gene (PTCH1), which is a tumor suppressor gene that is significant for embryonic structuring and cell cycle. Mutation in PTCH1 is responsible for the development of this syndrome (4-6).

The syndrome involves many organ systems and, thus, there are many different signs and symptoms manifested (2). The clinical presentation of NBCCS include basal cell carcinoma (BCC) that can present as early as age 2, odontogenic keratocysts, which generally develop in the first, second or third decades, palmar and/or plantar pits and ectopic calcifications of the falx cerebri (2, 4). These manifestations are considered major criteria for diagnosis (2). Some of the minor criteria include, but are not limited to, macrocephaly, congenital malformation, such as cleft lip or palate, frontal bossing, skeletal deformities, such as sprengel deformity, marked pectus deformity, marked syndactily of the digits and medulloblastoma (4, 5). The diagnosis is made with the presence of two major criteria or one major plus two minor criteria (4).

Case Report

A 31-year-old male with no significant past medical or surgical history (other than cyst removal from gums and lasik eye surgery) presented with multiple facial nevi that had been present since age 11 (6th grade). The patient reported he never had lesions in other areas; however, approximately 5 years ago, he noticed increasing number of lesions and in the last 1-3 years had noted significant growth in size of the lesions. The patient reported occasional pus and mucus in his eyes and occasional bleeding from the lesions around the eyelid. The patient denied any treatment or surgical resection

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Key Words: Nevoid basal cell carcinomas, odontogenic keratocysts, palmar and plantar pits, intracranial calcifications.

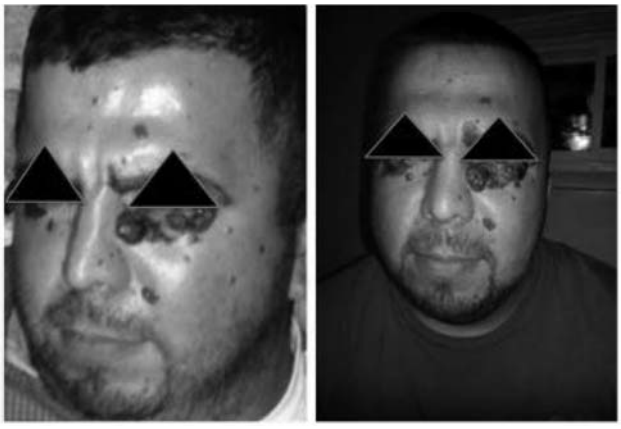

Figure 1. *Malignant facial BCCs prior to treatment.*

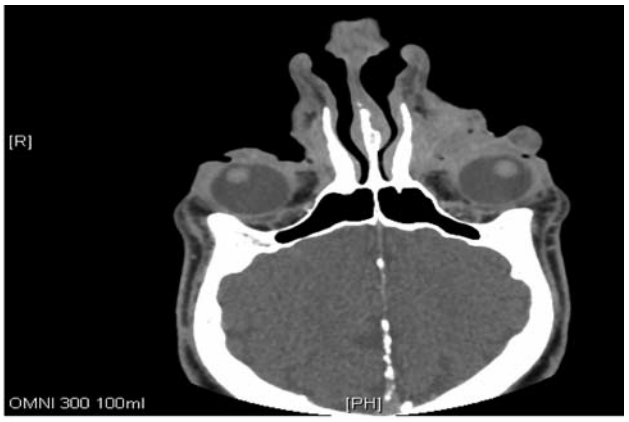

Figure 2. *Bilateral keratocystic odontogenic tumors in maxillary sinuses.*

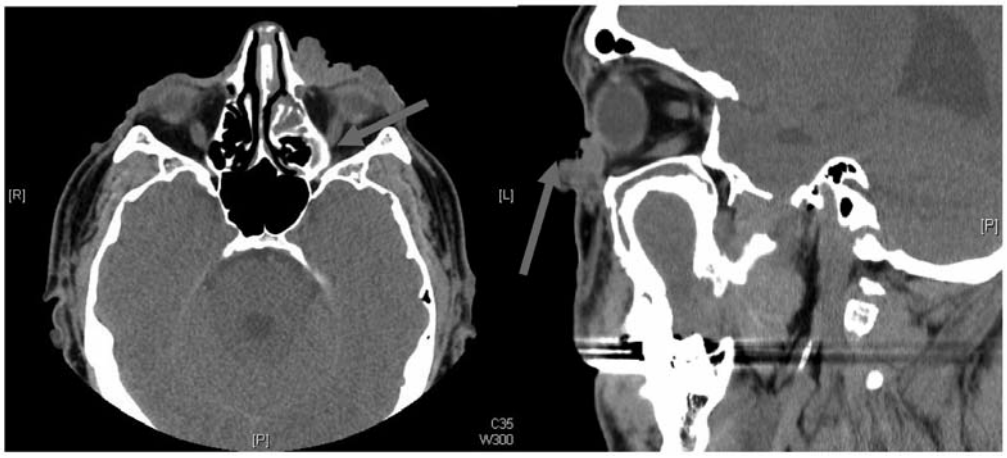

Figure 3. *Coronal view (left frame) and sagittal view (right frame) showing exophytic nodular soft tissue lesions of the left infra-orbital face.*

of the lesions in the past. On physical examination, there were notable multiple hyperpigmented exophytic nodular facial lesions of different sizes on the infra-orbital area bilaterally. These lesions were noticeably more pronounced on the left infra-orbital area (Figure1). The rest of the examination was unremarkable.

The patient had a computed tomography (CT) head/Maxillofacial scan that showed bilateral keratocystic odontogenic tumors of the maxillary sinuses (Figure 2). These tumors were in conjunction with exophytic nodular soft tissue lesions of the right infra-orbital face measuring 2.1×1.6×2.5 cm and near bilateral eyelids, as well as dural calcification (Figure 3). These imaging findings are consistent with basal cell nevus syndrome. The left maxillary sinus had thick calcified wall. There was an expansion of the left maxillary sinus with displaced molar teeth.

Histopathological findings. With the CT scan findings, we proceeded to a biopsy of the lower eyelids and anterior lamellae. The biopsy from the left lower eyelid showed a typical nodular-type BCC with nests of basaloid cells in the dermis (Figure 4). Peripheral palisading and cracking artifacts were seen. The biopsy from the right lower eyelid showed micronodular type BCC (Figure 5). The nests were small and infiltrative and did not exhibit peripheral palisading. A marked plasmacytic and lymphocytic response was present between the nests of tumor. The biopsy findings were consistent with BCC; therefore, the diagnosis of multiple BCCs and presence of the odontogenic cyst on imaging confirmed the diagnosis of NBCCS (Gorlin syndrome).

The patient's tumors were found to be unresectable at which time he was referred to the oncology clinic for medical management. The patient was started on vismodegib

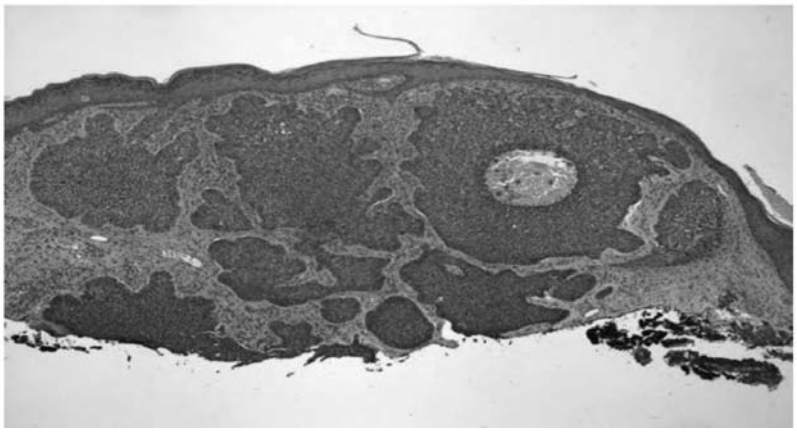

Figure 4. *The biopsy from the left lower eyelid showing a typical nodular type BCC with nests of basaloid cells in the dermis.*

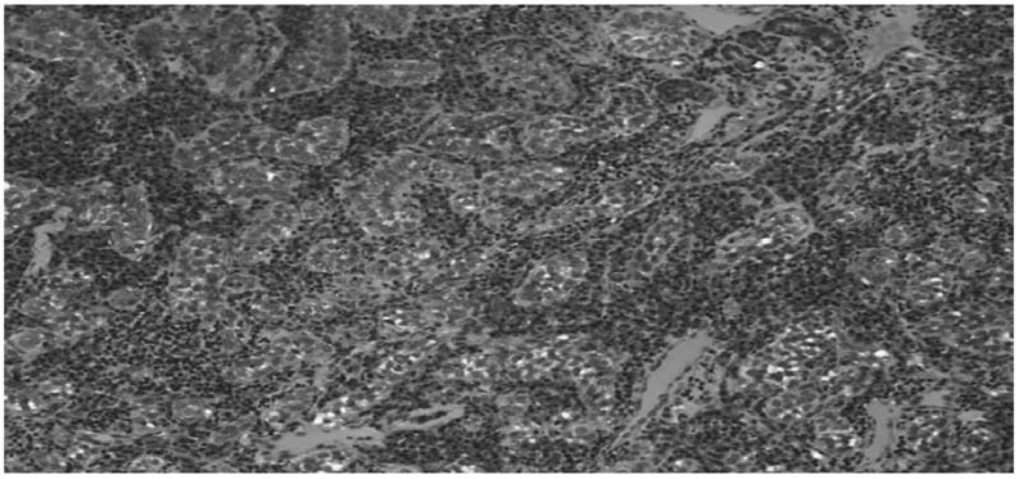

Figure 5. *The biopsy from the right lower eyelid showing micronodular-type BCC.*

150 mg by mouth daily. The patient tolerated treatment well and a significant change was noticed in facial lesions at one month and at four months after starting treatment. Figure 6 shows improvement of the facial lesions after 4 months of treatment with vismodegib. There was a significant reduction of the tumor in the left periorbital area and clearing of lesions on the right periorbital area. Currently, the patient is being maintained on this therapy.

Discussion

NBCCS, also known as Gorlin-Goltz syndrome, was first described by Jarish and White in 1894 but later recognized and established as an unique syndrome by Gorlin and Goltz in 1960 (1, 4).

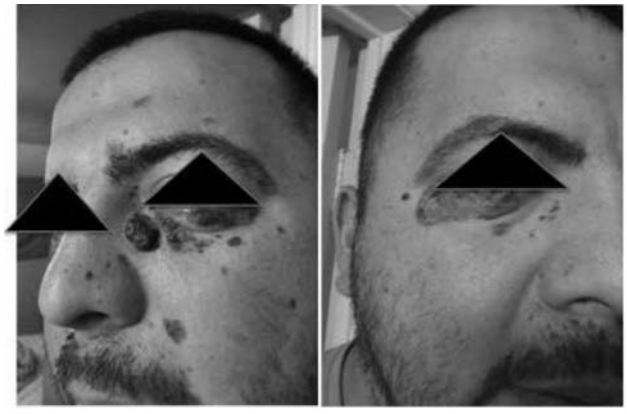

Figure 6. *Improvement of facial lesions after 4 months of treatment with vismodegib.*

The exact pathogenesis of this syndrome has not been completely elucidated but has been postulated to be caused by a mutation in a suppressor gene, *PTCH1*, which resides in the long arm of chromosome 9 (3, 4). *PTCH1* is a human homologue of Drosophila and a member of hedgehog signaling, a highly conserved pathway in vertebrates (1, 10). Since Hedgehog signaling regulates cell growth and development, a disorder of this pathway gives rise to not only developmental anomalies but also diverse tumors like those seen in NBCCS (4-6, 10).

The characteristic findings of NBCCS include multiple BCCs, palmar and plantar pits, jaw cysts, bony abnormalities and ectopic calcifications of the falx cerebri (1, 3, 4). The jaw cysts are usually the earliest features and are the most common stigma of the syndrome (3). Histologically, these cysts are ondontogenic keratocysts constituting one of the major criteria for diagnosis of NBCCS (1, 3, 4). The diagnostic criteria consisting of major and minor criteria were first established by Evans *et al*. and later modified by Kimonis *et al*. (4, 6).

Our patient met two major criteria for the diagnosis of NBCCS. He presented with advanced multiple BCCs and keratocystic odontogenic tumor of the maxillary sinuses. The patient developed multiple facial nevi during early childhood that increased in size and progressed to malignant lesions late in his second decade of life. Our patient presented late with multiple BCCs of the face that were not resectable.

Current first-line therapy for BCC consists of surgical removal and, potentially, radiation therapy (11). Most BCCs are cured by surgery but, in some cases, the cancer is not amenable to surgery and radiation is deemed cosmetically disfiguring (11). These are considered locally advanced BCC (laBCC) and may metastasize without treatment. Non-surgical treatment options include photodynamic therapy, topical imiquimod or 5-fluorouracil (11). These treatment modalities were not US Food and Drug Administration (FDA)-approved for these cases, thus providing median survival rate of six months to 3.6 years for metastatic disease (12).

In the beginning of 2012, after completion of a phase II clinical trial (13), vismodegib became the first drug approved by FDA for the treatment of locally advanced and metastatic BCC. This novel drug also introduced a new signaling target in the treatment of cancer, the Hedgehog (Hh) pathway. Most of the targeted oral agents approved to date are classified as tyrosine kinase inhibitors. Prior systemic treatment recommendations consisted of platinum-based therapy (cisplatin or carboplatin) or palliative and supportive care (14).

Vismodegib binds and inactivates smoothened (SMO) and inhibits its translocation when PTCH1 is stimulated by Hh ligand (11). Inhibition of the Hh pathway results in decreased downstream production of proliferation factors ultimately leading to suppression of BCC growth (11). The FDA-approved dosing of vismodegib is 150 mg orally daily until disease progression or unacceptable toxicity is experienced. The most common reactions are muscle cramps, alopecia, dysgeusia, weight loss and fatigue.

The patient was started on vismodegib, which he tolerated well, and a significant change was noticed on facial lesions only after a few months of starting treatment. Although our patient has not shown any signs of resistance thus far, there are a few reported cases of resistance after patients initially responded to therapy and then resistance developed (11, 15). One case report described a 26-year-old man with treatment-refractory metastatic medulloblastoma who developed resistance after 3 months, despite an initial response (16). In this patient's case, it was observed that a D473 resistance mutation had occurred in *SMO* that prevented vismodegib binding, thus losing efficacy against the tumor (11).

Dijkgraaf *et al*. performed further investigation into the mechanisms of resistance to vismodegib through simulation of the mutation (17). They substituted every amino acid for the aspartic acid at position 473 and vismodegib binding was assessed (17). It was determined that all mutant variations were less sensitive to vismodegib than wild-type SMO (11). The study also elucidated that E518 is an important residue in vismodegib activity on SMO and its mutation-conferred complete resistance to vismodegib.

The second case showed a complete clinical response after 5 months of treatment but a subsequent progression after 11 months on vismodegib (15). It was demonstrated by an *in silico* analysis that SMO G497W undergoes a conformational rearrangement resulting in a partial obstruction of the protein drug entry site, whereas the *SMO* D473Y mutation induces a direct effect on the binding site geometry leading to a total disruption of a stabilizing hydrogen bond network (15). Thus, the G497W and D473Y *SMO* mutations may represent two different mechanisms leading to primary and secondary resistance to vismodegib, respectively (15).

Vismodegib is the first FDA-approved agent for the treatment of unresectable BCCs. Our patient was started on this agent and has responded well thus far. Although vismodegib shows some promising clinical results on unresectable BCC in the early phase of treatment, there is evidence in the literature of evolving resistance to the agent later on in treatment. Duration of therapy, role of maintenance treatment and drug modification to reduce resistance need to be explored in future case studies.

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