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A Novel PTCH1 Mutation in Patient with Gorlin-Goltz Syndrome and its Management, A Case Report

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Case Report

Gorlin-Goltz syndrome (GS), also known as nevoid basal cell carcinoma syndrome or basal cell naevus syndrome, is a rare autosomal dominant hereditary disease characterized by systemic and diverse developmental abnormalities and neoplastic lesions [1]. Patients with Gorlin-Goltz syndrome develop commonly multiple odontogenic keratocysts around the age of 20, and basal cell carcinomas (BCCs) especially in middle-aged patients. The diagnosis of GS is based on clinical, radiological, and genetic elements. The criteria reported by Kimonis et al. [2] are the most used. This method includes six major criteria: basal cell carcinoma, palmar plantar small depression, jaw bone cyst, rib abnormalities, calcified falx cerebri, and family history of the disease within the first degree; and six minor criteria: macrocephaly, ovarian fibromas, congenital malformation, skeletal abnormalities, X-ray abnormalities, and medulloblastomas. Follow these criteria, we can make a diagnosis when the patient presents two major criteria, or one major and two minor criteria [2]. The confirm of the diagnosis is related to gene mutation analysis. So genetic counseling is mandatory after genetic diagnosis. PTCH1 is a tumor suppressor gene is the most common mutated in Gorlin-Goltz syndrome. A frameshift mutation is the most frequently, followed by nonsense mutation; the result is a premature termination of PTCH1 translation. PTCH1 is placed on the long arm of chromosome 9 (9q22.32) and it is made of 23 exons [3-4]. It is an a 12-transmembrane domain membrane protein with a pivotal role in ligand recognition, and it is a member of the RND transporter family. It presents also the TM2-6 bundle, a sterol sensing domain which is supposed to have interactions with Hedgehog ligands [5]. Surgical excision with free margins represents the gold-standard treatment for the majority of BCCs; in some forms of BCC radiotherapy, cryotherapy, electrodesiccation and curettage, photodynamic therapy, or the use of topical treatments (5-fluorouracil or imiquimod) could be used as alternative treatments considering the size, subtype and possible cosmesis outcomes [6]. Often neither surgery nor radiotherapy is a valid option for the treatment of some BCCs that are classified as 'difficult-to-treat BCCs', supporting the need of alternative systemic therapies. Vismodegib and sonidegib are two targeting oral treatments approved by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of advanced BCCs. Specifically, vismodegib is indicated both in laBCC and mBCC, while sonidegib only in laBCC. These therapeutic agents both act by inhibiting SMO receptor, thus deactivating the Hedgehog pathways and blocking the oncogenesis process [7]. Here we present the case of a sixty-year-old woman who has a medical history of basal cell carcinomas from the age of forty. To date she has undergone more than thirty surgical interventions to remove basal cell carcinomas. She has also rib and skeletal abnormalities and jaw bone cist. The genetic analysis was performed with the patient's consent, and it evidenced the presence of a duplication of the 2 and 3 exons of PTCH1 gene in heterozygosis. So, we could confirm the diagnosis of Gorlin-Goltz syndrome. Unexpectedly, the patient also developed a cutaneous squamous cell carcinoma in 2019 treated with surgery. In July 2022 she came for the follow-up visit and she presents more than 20 BCC of which 3 locally advanced (la) BCC. The patient denied a more surgical or radiotherapy treatment, so we

evaluated the systemic approach with sonidegib since there were no contraindications. The patient approved this oral therapy, so we acquired the relative informed consent, and we start sonidegib 200 mg/die. After only 3 months of therapy, at the follow-up in October 2022, the patient showed a reduction up to the 40% of its BCC without any side effect. This case report evidences the peculiarity of the Gorlin-Goltz syndrome: the association between basal cell carcinomas and multiple systemic alterations such as rib and skeletal abnormalities and jaw bone cist. So, we want to underline the importance of the new mutation that we found which consist in the duplication of exons 2 and 3 of PTCH1 gene. To date, as regards this type of mutation, only 8 exon [8] and 10-17 exons duplication [9] have been descripted in literature. This demonstrates the necessity of future studies through which enhance the knowledge about the pathogenesis of the clinical features of this syndrome; maybe relating the different mutations of PTCH1 to each phenotype to improve the promptness of the most suitable treatment. By the way, a systemic treatment could be an interesting approach in patients with Gorlin-Goltz syndrome in the perspective of treat the multiple BCCs that they present and prevent the onset of new ones. So, our experience with sonidegib is an encouraging start for further studies, maybe involving more patients with a long term follow up to confirm our findings.

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