

# NEW MEDICAL AND SURGICAL FINDINGS IN MULTIDISCIPLINARY APPROACH OF GORLIN-GOLTZ SYNDROME

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## SUMMARY

**Objectives.** Gorlin-Goltz syndrome (GGS) is a rare autosomal dominant disorder. The disease shows multiple organ involvement with variable clinical presentation. A multidisciplinary approach is required for its prompt clinical diagnosis and management. The diagnosis of the syndrome was based on its clinical presentation, radiological features and histopathological findings.

**Methods.** This paper highlights a surgical and medical treatment of a case of GGS. A 42-years-old Italian female, affected by GGS, was referred to our surgical department for evaluation of multiple naevoid basal cell epithelioma and recurrent radiolucent jaw lesions. The syndrome was diagnosed based on its clinical presentation, radiological features and histopathological findings.

**Results.** Removal of basal cell carcinomas and enucleation of the jaw cysts along with chemical cauterization with Carnoy's solution were performed under general anesthesia. In the left side a mandibular resection BRC according to Urken classification was necessary, and a free fibula flap through a minimally invasive technique was harvested for mandibular reconstruction. During follow-up no sign of recurrence was detected, ongoing implant oral rehabilitation.

**Conclusion.** Gorlin-Goltz syndrome (GGS) is a rare disorder. As we describe on the paper the disease shows multiple organ involvement with variable clinical presentation. We suggest a multidisciplinary approach for its prompt clinical diagnosis and management.

**Key words:** Gorlin-Goltz syndrome (GGS), epithelioma, fibula, vismodegib.

## Introduction

Gorlin-Goltz syndrome (GGS) is an autosomal dominant disorder with extremely variable manifestations. It is a rare disease that is characterized by multisystem involvement, with a predisposition to cysts, neoplasms and other developmental abnormalities (1). In 1894 Jarisch and White were the first to describe the essential features of this syndrome and termed it as nevoid basal cell carcinoma syndrome (2, 3). Almost a century later, in 1960, Gorlin and Goltz delineat-

ed different clinical features of GGS in their paper on “multiple naevoid basal cell epithelioma, jaw cysts and bifid rib syndrome” (4). The usual characteristic features of GGS include multiple keratocystic odontogenic jaw tumor, basal cell carcinoma, bifid ribs, palmar/plantar pits and calcification of the falx cerebri. Along with these, numerous other features have been reported in literature, including developmental deformities like; macrocephaly and cleft lip/palate, facial features like; frontal bossing and hypertelorism, skeletal abnormalities, and tumours including ovarian fibroma and medulloblastoma.

With a background of the variable presenting features, Evans et al. enumerated major and minor criteria for diagnosis of the syndrome. This was later modified by Kimonis et al. in 1997, who stated that in order to establish diagnosis of GGS, at least two major and one minor or one major and three minor criteria must be present (5). The management of patients with GSS requires a multidisciplinary approach that combines surgical and medical therapies. The treatment plan should be tailored in a case-by-case manner in order to obtain the best morphological and functional result with less invasiveness and morbidity. Today we can count on CAD/CAM technology to achieve the best accuracy in facial reconstruction. As we later describe in this case, we combined a medical approach with Vismodegib available in the US and several European and Asian countries. In Italy it is indicated for treatment of adult patients with metastatic BCC, or with locally advanced basal cell carcinoma where surgery and/or radiation therapy are not appropriate with high satisfaction rate.

## Case report

A 42-years-old Italian female, affected by GGS, was referred to our surgical department for evaluation of multiple naevoid basal cell epithelioma and recurrent radiolucent jaw lesions. The syndrome was diagnosed based on its clinical presentation, radiological features and histopathological findings. The patient's medical history revealed left UCLP treated in another hospital (both primary cheilorhinoplasty/palatoplasty either secondary orthognathic surgery). On facial examination results of correction of left cleft lip, scars of previous removal of multiple BCC and multiple naevoid basal cell epithelioma (Figure 1). Intraoral examination showed left jaw swelling and loss of multiple dental elements. The orthopantomography of the patient revealed Le Fort I osteotomy completed for maxilla hypoplasia, multiple radiolucent lesions involving the mandible, in particular the left side was involved with completely subversion of the body

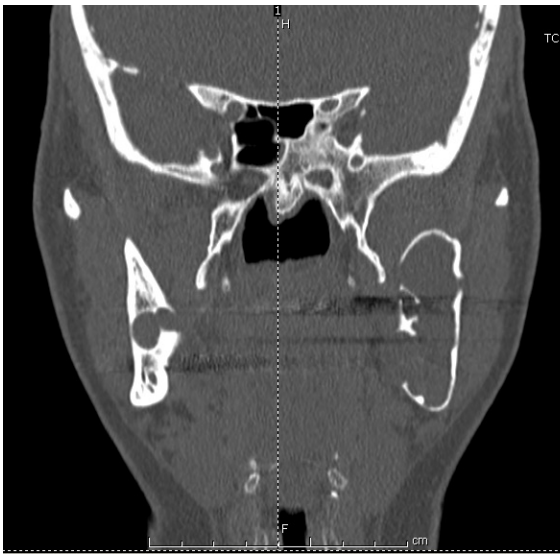


**Figure 1**  
Pre-op picture with multiple naevoid basal cell epithelioma.

and the ramus (Figures 2, 3). Posterior-anterior and lateral view of the skull taken to study skeletal discrepancies showed calcification of falx cerebri (Figure 4). Chest, limb and cervical spine radiographs showed no abnormality. Computed tomography (CT) of facial bones and cranium was advised for detailed radiological assessment and for treatment planning. Sectional CT views showed a large well defined expansile lesion with corticated margins of about 5.5 cm in size involving the left mandible body



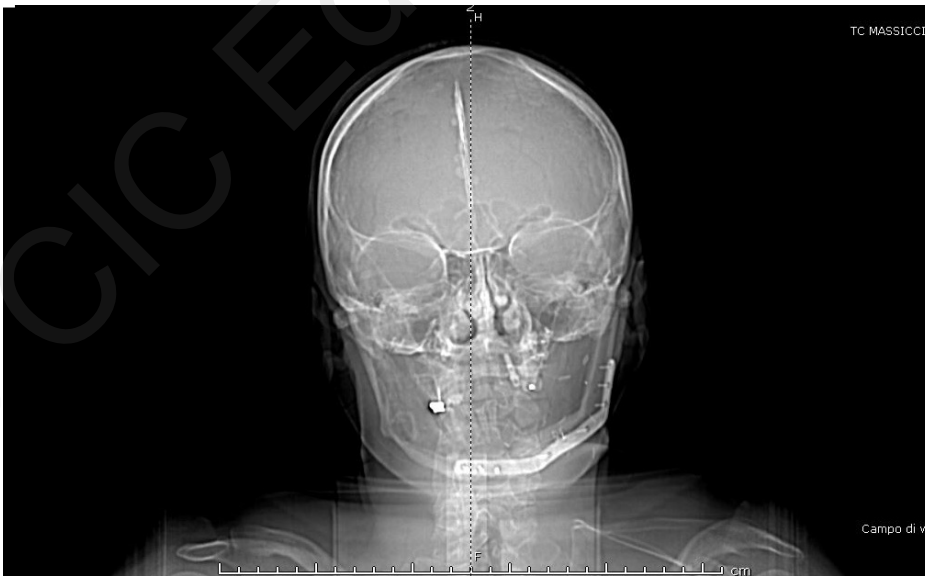
**Figure 2**  
Axial TC multiple cystic lesion of the mandible.



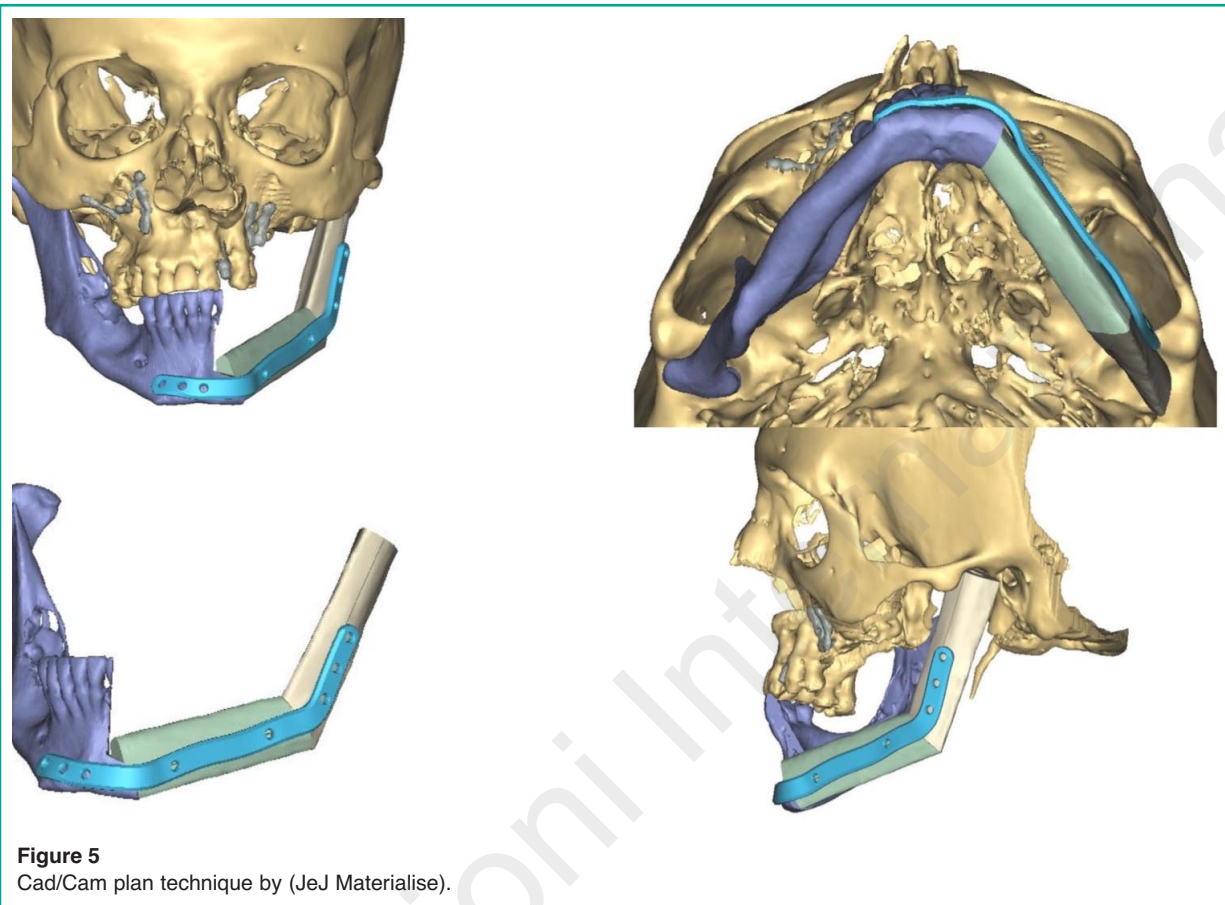
**Figure 3**  
Coronal TC multiple cystic lesion of the mandible.

and ramus region. Multiple similar lesions were noted in the angle on the right mandible. Multiple calcifications along the falx cerebri and tentorium cerebelli were seen (Figure 4). The above dental, skeletal, cranial and dermatological features were suggestive of GGS with multiple jaw cysts. Incision biopsy of jaw cyst was carried under local anesthesia. Histo pathological study

of the specimen showed epithelium suggestive of keratocystic odontogenic tumor (KCOT). Removal of basal cell carcinomas and enucleation of the jaw cysts along with chemical cauterization with Carnoy's solution were performed under general anesthesia. In the left side a mandibular resection BRC according to Urken classification was necessary, enucleation was not enough safe to guarantee a radical removal, the KCOT was widespread blowing and interrupting the jaw cortical bone and a free fibula flap through a minimally invasive technique (15, 17) was harvested for mandibular reconstruction. For greater accuracy, the reconstruction was designed and implemented using a CAD/CAM technique (JeJ Materialise) (Figure 5) (7). A high resolution TC of the maxillary bone of the mandible associated with a Tc scan of the lower limbs vascularization were performed to ensure feasibility. It was decided for a rhino-tracheal intubation; no tracheotomy was necessary. Intraoral accesses were preferred to dominate the removal of the cystic lesions. Two cutaneous accesses, submandibular and pre-auricular, were performed to complete the micro vascular anastomoses and to verify the condylar position. No local and systemic complications on the donor site was detected during follow-up (14). Microscopic evaluation of the specimen



**Figure 4**  
Calcification of falx cerebri.



**Figure 5**  
Cad/Cam plan technique by (JeJ Materialise).

lining was consistent for diagnosis of multiple KCOT.

Advanced and non-surgical BCC were treated with vismodegib (11), the application of this therapy was effective in reducing the morbidity of the surgical site and the hospitalization time of the patient (7) (Figure 6).

During follow-up no sign of recurrence was detected, ongoing implant oral rehabilitation (16, 22-25) (Figure 7).

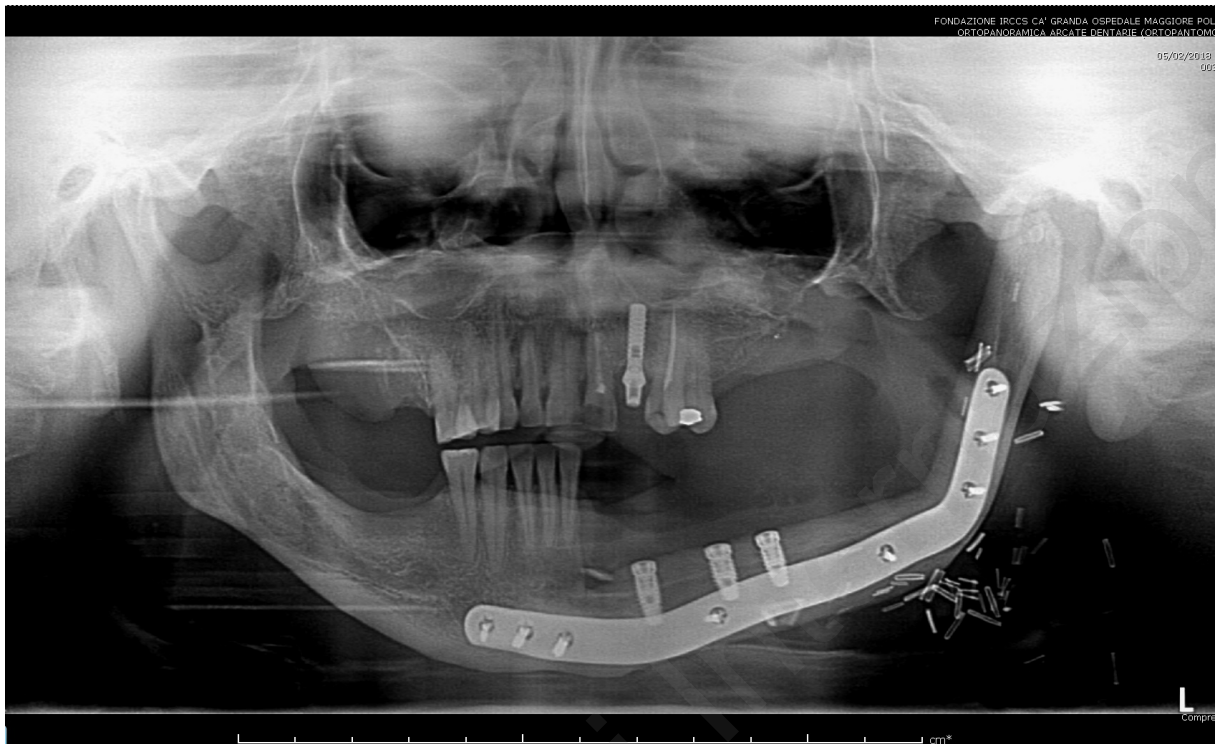
## Discussion

Gorlin-Goltz syndrome (GGS) is a rare genetic disorder with extremely variable manifestations. The prevalence of the disease range from 1 in 57,000 to 1 in 2,56,000 in the general population. It is caused by genetic mutation of the



**Figure 6**  
Orthopantomography.

PTCH1 gene present on the long arm of chromosome 9. The mutation is transmitted in an autosomal dominant manner from parent to sibling.



**Figure 7**  
Follow.up.

However 35 to 50% of GGS arises from spontaneous mutation, without any family history (7). More than 225 mutations in the PTCH1 gene in Gorlin-Goltz syndrome have been identified so far. The PTCH1 gene functions in production of patched-1 protein plays a role in cell growth and specialization. Mutation in this gene prevents the production or leads to the production of an abnormal protein that cannot effectively suppress cell growth and division. This results in an abnormal cellular proliferation resulting in formation of cyst/tumors that are characteristic of GGS. In the present report the patient had no family history and GGS was possibly due to spontaneous mutation. As with any syndrome, GGS is grouping of recognizable characteristics that occur together and have a common cause (i.e. mutation of PTCH1 gene). The clinical manifestations of GGS are highly variable with involvement across the organ systems. Evans et al. established the major and minor criteria for the diagnosis of the syndrome, which was later

modified by Kimonis et al. in 1997 (5).

The major clinical criteria includes more than two basal cell carcinoma or one basal cell carcinoma under the age of 20 years, KCOT, three or more cutaneous palmar or plantar pits, bifid/fused/splayed ribs and first degree relative with GGS. The minor criteria include: macrocephaly, cleft lip or palate, frontal bossing, hypertelorism, skeletal abnormalities (Sprengel deformity, marked pectus deformity, marked syndactyly of the digits), bridging of the sella turcica, hemivertebrae, flame shaped lucencies of the hands or feet, ovarian fibroma and medulloblastoma. To establish a diagnosis of GGS, two major and one minor or one major and three minor criteria must be present (Table 1). Two of the major features; multiple KCOT, more than two basal cell carcinoma and cleft lip and palate were positive for the present case. Other features incidentally noted were calcification of falx cerebri and tentorium cerebelli. The principal clinical features of GGS comprise a triad of

**Table 1** - Diagnostic Criteria.**Major criteria**

More than two BCC or one BCC under the age of 20 years  
 KCOT of the jaw  
 Three or more cutaneous palmar or plantar pits  
 Bifid, fused or markedly splayed ribs  
 First degree relative with GGS

**Minor criteria**

Macrocephaly  
 Cleft lip or palate, frontal bossing, hypertelorism  
 Skeletal abnormalities: Sprengel deformity, marked syndactyly of the digits  
 Bridging of the sella turcica, hemivertebrae, flame shaped lucencies of the hands or feet  
 Ovarian fibroma  
 Medulloblastoma

basal cell carcinoma (BCC), multiple KCOT and skeletal anomalies, particularly of the thoracic cavity. Cutaneous BCC are the most frequent skin lesion of GGS. It is more frequent in white population (80%), compared to blacks (38%). Epidemiological studies suggest that sunlight, and particularly UV radiation, is a strong risk factor for the formation of BCC. It has recently been demonstrated that UV irradiation enhances BCC development in mice with PTCH gene mutation, thus confirming that BCC development in GGS patients is enhanced by UV irradiation. Sites mostly affected are thoracic and cervico-facial skin surfaces, periorbital areas, eyelids, nose, malar region, and upper lip.

Another hallmark of GGS is occurrence of multiple KCOT of jaw (8). Multiple KCOTs are the most consistent and representative signs of GGS in the first and second decades of life. Like in the present case, jaw cysts may be found as an incidental radiographic finding, during dental treatment. However, it may clinically manifest as pain if the cyst is infected or cause symptoms such as swelling. KCOTs associated with GGS usually occur at an early age, usually in the first decade of life. In present case four cysts were discovered on orthopantomogram, occupying all the quadrants of jaw. KCOT are known to have a higher rate of

recurrence. However, the recurrence rate of KCOT in GGS is difficult to interpret because of the potential to develop multiple new cysts that occasionally may be confused with recurrence. Palmar and plantar pits are another major diagnostic clinical feature of GGS. These are multiple punctiform brownish black depression ranging from 2 to 3 mm in diameter and 1 to 3 mm in depth. Cutaneous pitting is caused by partial or complete absence of stratum corneum or dense keratin in sharply defined areas. It appears in 30-65% of patients of GGS by the age of 10 years and in 85% of patients over the age of 20 years. Various skeletal anomalies reported to be associated with GGS include high and broad forehead, frontal and parietal bossing. Facial features of broad nasal root are common and may be associated with ocular hypertelorism. As in this case the maxilla may be hypoplastic and there may be mandibular hyperplasia with variable prognathism. Other less common skeletal anomalies include a high arched palate, cleft palate and lip, malocclusions, multiple impactions of teeth. Considering the therapeutic approach, there are many innovations in clinical and surgical sense. To restore mandible contour, we decide to use a free fibula flap, first describe by Hidalgo (6), which has proved highly efficiency and functional for

mandibular reconstruction (12, 18, 19, 21, 22, 26). We decided to virtually plan the treatment with CAD/CAM design using a 3D software, Materialise. Through a web meeting surgeons obtained cutting guides for the mandible and the fibula, custom titanium plates to synthesize the bone stumps in the right position. As shown in many papers (7), this has proved capable of obtaining high levels of accuracy with the project obtaining a satisfactory final result in terms of morphological and functional restoration.

Better understanding of the molecular basis for, and aberrant pathways, involved in the pathogenesis of BCC, has resulted in a new targeted approach to therapy. Inhibitors of the hedgehog signalling pathway have shown great promise in the treatment of advanced BCC. The first of these to be approved, vismodegib (Erivedge®, Roche), is available in the US and several European and Asian countries. In Italy it is indicated for treatment of adult patients with metastatic BCC, or with locally advanced basal cell carcinoma where surgery and/or radiation therapy are not appropriate with high satisfaction rate.

## Conclusion

Gorlin-Goltz syndrome (GGS) is a rare disorder. As we describe on the paper the disease shows multiple organ involvement with variable clinical presentation. We suggest a multidisciplinary approach for its prompt clinical diagnosis and management (13, 20). There are many innovations in clinical and surgical approach that must be considered in certain and specified cases.

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