

Oral management of Gorlin-Goltz syndrome (nevoid basal cell carcinoma syndrome): case report and review article

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Abstract

A 62-year-old male with Gorlin-Goltz syndrome (GGS) who experienced multiple nevoid basal cell carcinomas and was receiving vismodegib presented for dental care. This case highlights the importance of a tailored treatment plan between the chemotherapy cycles for a patient diagnosed with GGS.

Key words: Gorlin-Goltz syndrome, nevoid basal cell carcinoma (NBCC), vismodegib, odontogenic keratocysts, dental extraction, Special Care Dentistry

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Introduction

Gorlin-Goltz syndrome (GGS) is a rare autosomal dominant condition that occurs as a result of gene mutation, specifically the PTCH gene, on chromosome arm q9 (Kimonis *et al.*, 1997; Pandeshwar *et al.*, 2012). It is also called nevoid basal cell carcinoma syndrome (NBCCS) (Casaroto *et al.*, 2011). Incidence reports vary from 1 in 57,000 (Farndon *et al.*, 1992), to 1 in 164,000 of the population (Shanley *et al.*, 1994).

The first case reported in 1894 was in a patient diagnosed with scoliosis, multiple nevoid basal cell carcinoma and a learning disability (Pandeshwar *et al.*, 2012). The syndrome of the classical triad of recurrent odontogenic keratocysts, bifid rib and nevoid basal cell carcinoma was described by James Gorlin and William Goltz in 1960 (de Amezaga *et al.*, 2008). Rayner *et al.* later added calcification of falx cerebri, palmar and plantar pits as other features of the condition (Rayner *et al.*, 1977).

Diagnosis is based on the minor and major clinical and radiological findings, confirmed by DNA analysis (Kalogeropoulou *et al.*, 2009). Two major or one major with two minor criteria are required for the diagnosis (Kimonis *et al.*, 1997), Table 1.

Case report

A 62-year-old male with GGS (Nevoid Basal Cell Carcinoma Syndrome) was referred to the Department of Sedation and Special Care Dentistry from the Oncology department at Guy's Hospital (London), for stabilisation of his oral health prior to his next cycle of vismodegib. Since the patient was diagnosed with NBCC, he has been on a 3-monthly review with the oncology team for any lesions suspicious for NBCC.

Chief complaint

The patient's chief complaint was dental pain related to the lower left mandible. He reported the presence of mobile teeth on the lower left area, which complicated his normal eating patterns.

Medical history and current medication

This patient had undergone more than 100 skin biopsies for NBCC lesions (Figure 1). Previous treatment included surgery, cryotherapy, peri-ocular and nasal Mohs surgery. He was also on a 3-monthly review to monitor for any lesions

Table 1: Major and minor criteria for the diagnosis of Gorlin-Goltz syndrome. (Kimonis *et al.*, 1997).

Criteria	Clinical signs
Major	• Nevoid basal cell carcinoma (more than two), or one nevoid basal cell carcinoma at age <30 years • Odontogenic keratocysts • Three or more palmar or plantar pits • Bifid, fused or markedly splayed ribs • Calcification of falx cerebri
Minor	• Macrocephaly, scoliosis, syndactyly, polydactyly, shortened 4th metacarpal • Radiological abnormalities - bridging of sella turcica • Medulloblastoma • Ovarian fibroma • Congenital malformations: cleft lip or palate, polydactylism, eye anomalies (cataract, coloboma, microphthalmus)

Figure 1: A nevoid basal cell carcinoma measuring 10 mm.

suspicious for NBCC in the skin and to plan cycles of vismodegib as appropriate.

Social history

Socially, the patient reported being a non-smoker. Additionally, he never drank alcohol. He was not working due to multiple medical appointments between ophthalmology, physiotherapy and oncology.

Dental history and dietary habits

The patient was registered with the Community Dental Service (CDS) but the medical appointments made attendance irregular. He brushed his teeth three times daily using Duraphat® toothpaste (5,000 ppm). The patient reported multiple odontogenic keratocysts removed from the jaws before the age of 23 years. He was on soft diet, mainly vegetables and rice with one cup of tea every day, with no additional sugar.

Clinical examination

Extra-oral findings showed average body stature, complete alopecia related to vismodegib and multiple scars on the face related to previous surgery for NBCC. Intra-oral examination showed poor oral hygiene, retained roots, generalised mild gingivitis, periodontitis and moderately dry mouth based on the Challacombe scale (Osailan *et al.*, 2012). Basic Periodontal examination (BPE) scored 3 in each quadrant. An asymptomatic bony swelling in the anterior part of the hard palate related to the pre-maxilla was also noted. Figures 2 and 3 show the pre-treatment clinical photographs.

Ethyl chloride was applied to maxillary teeth. The responses indicated that all the retrograde filled teeth with amalgam and the lower right premolar were non-vital (see the radiographic examination below).

Dental radiology reported a large radiolucent bony defect in the apical area extending from the upper right first premolar to the upper left canine with evidence of multiple apicectomies with retrograde amalgams (without orthograde root canal treatment of teeth) and periapical radiolucencies suggestive of periapical infections. This was likely to be due to periapical dental infection associated with the teeth (Figures 4 and 5).

Odontogenic keratocysts have a high recurrence rate (Khaliq *et al.*, 2016; Kiwilsza and Sporniak-Tutak, 2012). Therefore, cone-beam computed tomography (CBCT) was used as a diagnostic instrument for precise assessment of the potential recurrence of any odontogenic keratocysts. The CBCT revealed extensive dental disease (bony destruction as

Figure 2: Maxillary view showing palatal swelling of pre-maxilla.



a result of unsuccessful endodontic treatment) with no evidence of keratocysts in the jaws (*Figures 6a-b*). Different approaches to deal with this disease were proposed.

Aims of dental treatment

The aim of treatment was to relieve dental pain, to prevent dental infection and stabilise oral health status prior to a new cycle of vismodegib.

Short term treatment plan

This was for routine dental advice including oral hygiene instructions, use of interdental brushes, diet advice and prescription of sodium fluoride toothpaste (Duraphat® 5,000 ppm). Further treatment planned included scaling and polishing, dental extraction of the infected roots of the lower left lateral incisor and lower left second molar teeth,

Figure 3: Frontal view showing challenging occlusion related to GGS.



dental restoration of upper left first molar, root canal treatment of lower right second premolar and construction of a lower partial denture. The complexity of treatment, need for multiple dental visits and the limited time prior to starting a cycle of vismodegib were discussed with the patient.

Prior to starting any dental procedure, the patient's treatment was discussed with a maxillofacial radiologist, an oral surgeon and an endodontist. Advice was taken on the possible recurrence of odontogenic cysts and treatment of the teeth with apicectomies. Furthermore, the patient's oncologist had been consulted to check the full blood counts, coagulation screen and the effect of the vismodegib on healing and haemostasis.

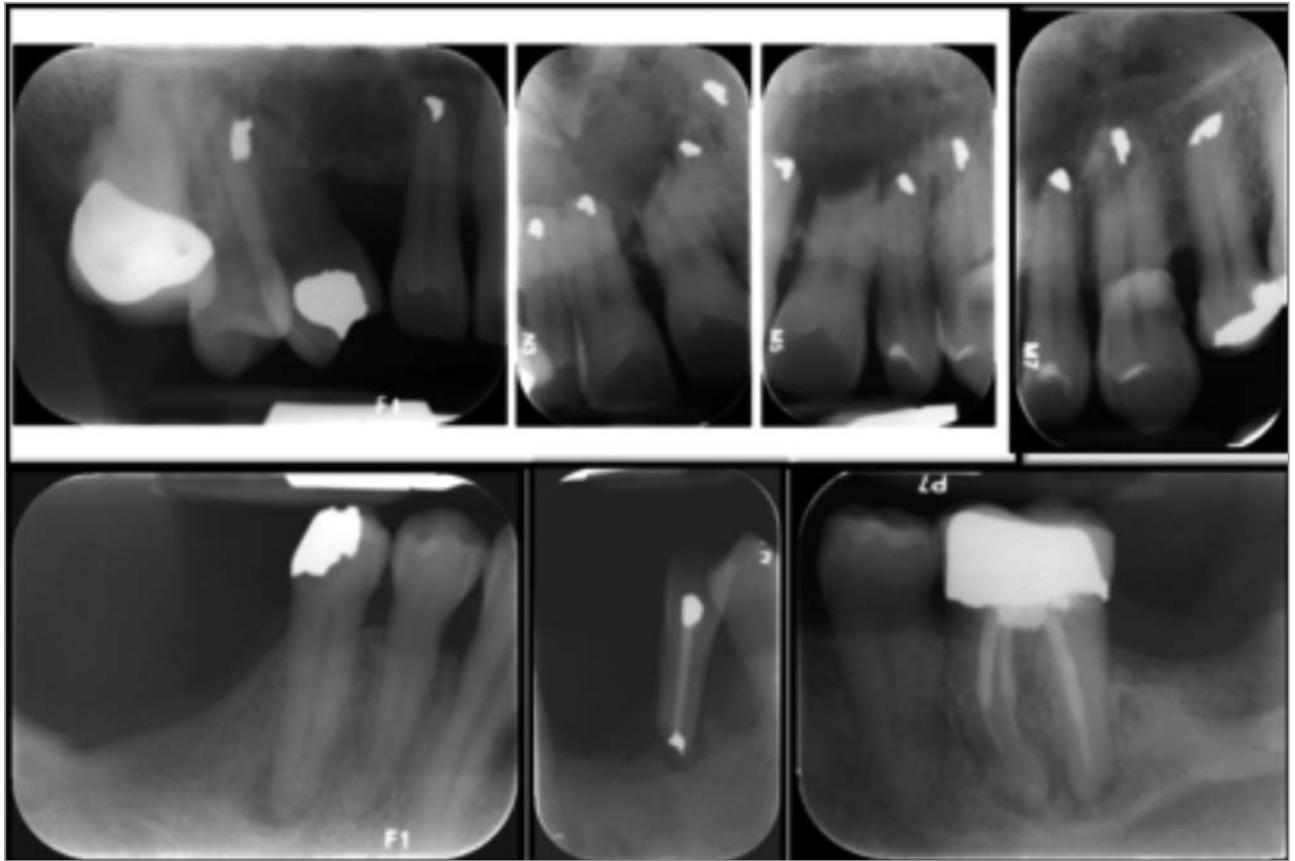
Treatment choices were made by the patient and the development of a new skin NBCC restricted dental treatment to stabilising the oral health status without complex treatment, prior starting the new cycle of vismodegib. *Figure 7* shows post-treatment photographs

Long term treatment plan and future care

The patient was booked for recall every 3 months on the same day as his oncology appointment for any lesions

Figure 4: Dental panoramic tomograph (DPT) requested to assess bony swelling and pathology, including abnormalities related to GGS.



Figure 5: Intra-oral periapical radiographs (IOPA) show previous apicectomies with retrograde root fillings.

suspicious of NBCC. He was also informed about his need to have dental extractions of maxillary teeth or root canal treatment with apicectomies post-vismodegib cycle.

Dental implications

Barriers to accessibility

One of the most challenging aspects of this case was deciding on the most appropriate treatment plan. The patient had multiple dental needs and required treatment in a limited time frame. Liaison with other specialties suggested differing treatment plans. One option considered was extraction of the affected teeth to eliminate infection and help avoid further damage. Alternatively, the Endodontic department advised orthograde root canal treatment followed by a surgical apicectomy.

Vismodegib

Vismodegib is a hedgehog pathway inhibitor, which regulates embryonic development, cell growth and differentiation (FDA, 2012). It is used in the treatment of locally advanced cancer such as NBCC. It was the first hedgehog pathway inhibitor presented in capsules of 150 mg under the brand name Erivedge® (Sekulic *et al.*, 2012). The typical dose is 150 mg once daily unless disease progression or unacceptable toxicity occurs (Sekulic *et al.*, 2012).

The effects of vismodegib on liver function and the risk of bleeding

Clinically, vismodegib is associated with a low or transient elevations in serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) during the active period of treatment and has been linked to rare cases of clinically apparent acute liver injury (Cirrone and Harris, 2012).

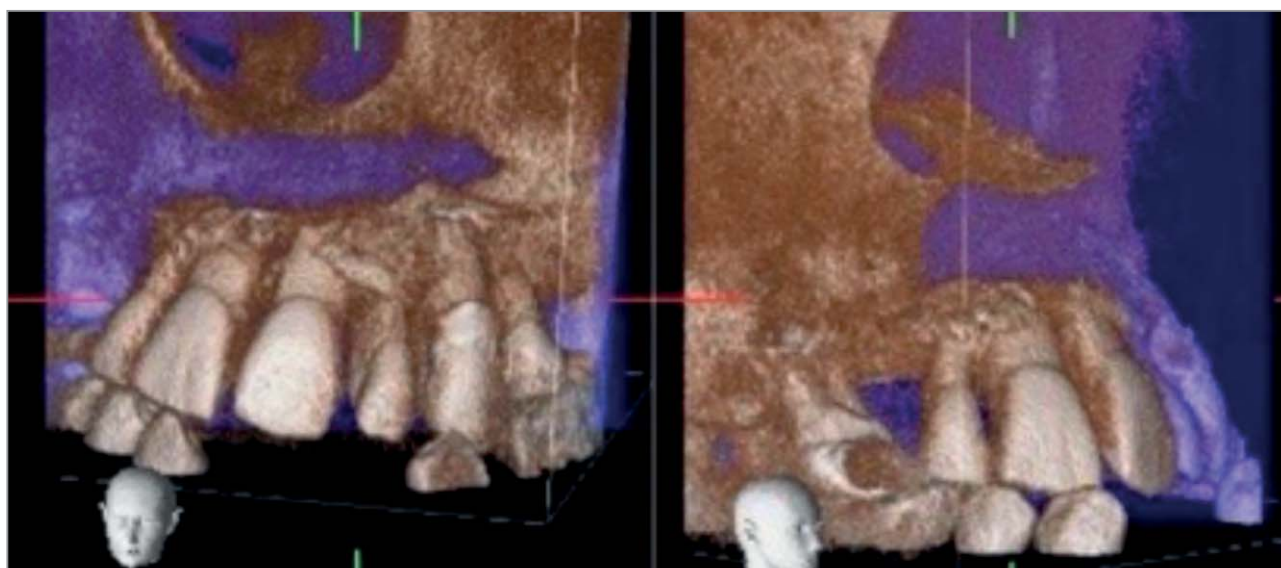
These enzymes are measured to see if the liver is damaged or diseased, in which case they are released into the bloodstream. This increases the likelihood of bleeding and would be a risk for dental procedures. Other common side effects include muscle spasms, alopecia, anorexia, dysguesia, weight loss, nausea, diarrhoea, fatigue and arthralgia (Sekulic *et al.*, 2012).

A subsequent revision of all reported studies of vismodegib reported liver enzyme elevation occurred in 1.4% of a total of 363 patients (NIDDK, 2017). The cause of liver injury from vismodegib is still unknown but likely due to hypersensitivity. Vismodegib has a prolonged half-life (approximately 19 days). It is metabolised in the liver via multiple cytochrome P450 enzymes (NIDDK, 2017).

Dental extraction for patients taking vismodegib

Vismodegib works, to some extent, differently from classical types of chemotherapy. However, the National Cancer Institute (NCI) recommends management of patients taking vismodegib is in accordance with their chemotherapy guidelines (NCI, 2011). The level of liver damage with

Figure 6a: 3D-reconstruction CBCT views showing destruction of labial maxillary alveolar bone from the maxillary right canine region to the maxillary left first premolar.



vismodegib is unpredictable. Caution is required prior to any invasive dental procedure that may induce bleeding. Therefore, it is advisable to have a coagulation screen (prothrombin time and partial thromboplastin time) and full blood count (especially platelet count) prior to surgical dental treatment. Non-invasive dental procedures such as supra-gingival scaling and simple dental restorations are usually not problematic and can be managed with local haemostatic measures such as topical use of tranexamic acid. No dental extraction should be performed if the platelet count is below $50 \times 10^9/L$, and no inferior alveolar nerve block is recommended if the platelet count is below $30 \times 10^9/L$. Any surgical procedures should be carried out with minimal trauma to both bone and soft tissues. Prior to more advanced surgery, medical advice should be sought.

Patients with platelet counts below $50 \times 10^9/L$ should be referred to a secondary care centre to be treated by a specialist in the Special Care Dentistry who will liaise with the patient's haematologist or oncologist for a platelet transfusion (Nizarali and Rafique, 2013, Scully *et al.*, 2007). The platelets transfusion may be given twice (prior dental extraction and after the end of the operation) or only prior to dental extraction. Sequestration of platelets is very rapid (Scully *et al.*, 2007); therefore dental extractions should be carried out within one-hour post-transfusion. One unit of platelets usually raises the overall count by $10 \times 10^9/L$ (Scully *et al.*, 2007). Dental extractions should be atraumatic and local haemostatic measures are recommended to help minimise bleeding, such as placement of sutures and using an absorbable haemostatic agent (Surgicel® oxidised regenerated cellulose). The patient may also be asked to bite on gauze soaked in tranexamic acid for 15-20 minutes following extraction to act as local antifibrinolytic agent. The patient should only be discharged after achieving haemostasis and given verbal and written post-extraction instructions.

Dental sedation of patient diagnosed with Gorlin-Goltz syndrome

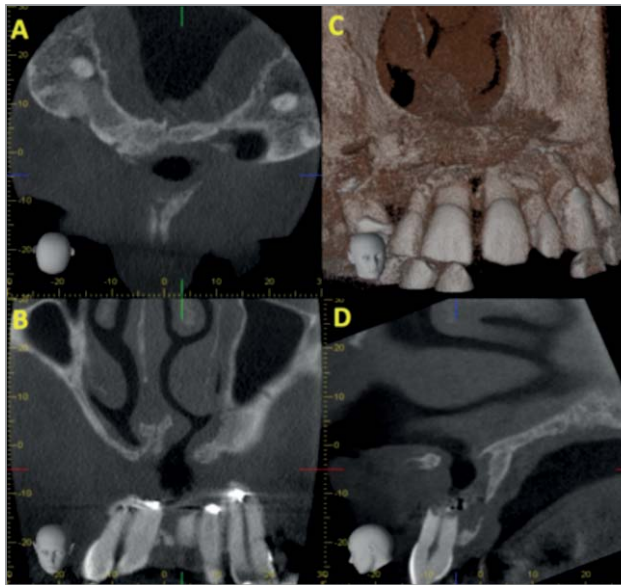
In the event of needing conscious sedation, any patient under treatment with vismodegib requires careful assessment. Vismodegib can cause liver damage, the effects of a sedative drug (i.e. midazolam) may be magnified due to changes in plasma protein concentration and small doses may produce exaggerated effects due to increased levels of free drug (Craig and Skelly, 2004). Metabolism may be very slow and recovery prolonged. Additionally, due to liver damage, the patient could be anaemic, conscious sedation should not usually be carried out when the haemoglobin level is less than $10g/dL$ (Scully *et al.*, 2006).

Recommendation

This case report emphasises the need for awareness of the diagnostic criteria of GGS, especially in cases with no typical skin lesions. Early diagnosis helps to reduce fatal consequences related to multiple NBCC and other anomalies associated with the disease, such as odontogenic keratocysts or spine and rib malformation (Ljubenovic *et al.*, 2007; Pandeshwar *et al.*, 2012). In the early stage, NBCC is sensitive to the treatment (Ljubenovic *et al.*, 2007).

The importance of using CBCT imaging during the assessment of cystic lesions in conjunction with a full DPT was also highlighted during this case, to avoid misdiagnosis of recurrent odontogenic keratocysts and to determine the proper management i.e. surgical enucleation with/without root canal treatment or follow up or watch and wait.

Figure 6b: Different plans of CBCT (A-axial, B-coronal, C-3D-reconstruction, and D-sagittal) revealed extensive destruction of the anterior pre-maxilla, particularly the labial bone. Sagittal plan shows communication to the nasal cavity at the level of 21.



The Royal of College of Surgeons clinical guidelines

The Royal College of Surgeons of England / British Society for Disability and Oral Health (RCS/BSOH) (2012) provide clear strategies and a clinical guideline for the oral management of oncology patients requiring radiotherapy, chemotherapy and/or bone marrow transplantation (RCS/BSOH, 2012). Pre-dental assessment is strongly recommended for any patients planning to start treatment of GGS with vismodegib to reduce future complications and to avoid the need of an invasive dental treatment during the active period of treatment. Prior to any invasive dental procedures, medical advice should be sought.

Conclusion

This case is a summary of a patient with Gorlin-Goltz syndrome (GGS) who required significant dental intervention. However, different variables played an important role in determining the accepted treatment plan for the patient and the special care dentist. The suggested treatment plan was minimally invasive to decrease the likelihood of complications and was influenced largely by the patient's choice to simplify treatment and reduce unnecessary psychological stress.

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Figure 7a-c: Post-treatment photographs: a) Showing dental restoration of the 26, b) showing root canal treatment of 45, c) showing lower partial denture



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