Author’s response to reviews

Title: Multidisciplinary oral rehabilitation of an adolescent suffering from juvenile Gorlin-Goltz syndrome - a case report

Authors:

Manfred Nilius (manfrednilius@niliusklinik.de)
Jürgen Kohlhase (j.kohlhase@humangenetik-freiburg.de)
Johann Lorenzen (Johann.Lorenzen@klinikumdo.de)
Günter Lauer (guenter.lauer@uniklinikum-dresden.de)
Matthias Schulz (matthias.schulz@uniklinikum-dresden.de)

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Author’s response to reviews:

Comments to the reviewer

Reviewer # 1

The reviewer has the following comments and questions:

The manuscript is organized, and generally well-written and coherent but lacking in some details. The topic will be of interest to the readers.

As you mentioned in 2005 this entity was changed from odontogenic keratocyst to keratocystic odontogenic tumor. However, within the manuscript you change in between the nomenclature, which will mislead your readers. KCOT should be clearly named as a tumorous lesion; consecutively the removal procedure should be called enucleation. This should be changed within the manuscript.

A: The authors thank the reviewer for this comment. Following the suggestion, the term “cystectomy” was replaced by “enucleation” throughout the manuscript.

Title - Consider changing the title to a declarative sentence that summarizes the key message of the manuscript.

A: The title of the manuscript has been changed into “Multidisciplinary oral rehabilitation of an adolescent suffering from juvenile Gorlin-Goltz syndrome – a case report” summarizing the main topic of the manuscript.
The abstract is clear and concise. However, you mentioned a new KOT in the maxillary sinus, which might not be of interest of your readers.

A: The authors think that it would be interesting to mention the KCOT in the maxillary sinus just to underline the frequency of occurrence.

The introduction contains an adequate review of literature on the subject. Nevertheless, the main problems in these young patients are 1) high recurrence rates, according to the histological diagnosis and subclassification (see also Jauernik et. al, Quinessence 2016), 2) the reduced donor site, donor site morbidity etc. 3) age and oral rehabilitation, which should be included in the introduction part. Therefore, a patient specific interdisciplinary treatment plan has to be considered.

A: The authors thank the reviewer for this comment. The following sentences have been inserted in the introduction section: “The aggressive pattern of growths and the tendency to recurrence require a thoroughly performed therapy depending on the histologic subclassification.” and “Considering the surgical management of extended bone defects in the adolescent two issues are challenging for the clinician: the rehabilitation with autologous bone is considered as golden standard (Khan 2005). However, a limited amount of autogenous bone and the donor site morbidity are factors limiting the use of autogenous bone (von Arx 2006). Furthermore, the age of the patient and the planned therapy of oral rehabilitation have to be considered. The placement of dental implants during the growths is currently an issue of discussion (Percinoto 2001). Thus, an individual treatment plan considering the age of the patient, the extend of the defects and the planned oral rehabilitation has to be created.“

Furthermore, additional literature has been inserted.

Case presentation section is concise. However, the reason and time point of the extraction of the teeth 46 and 47 is missing. Additionally, CBCT/ panoramic pictures of the serial augmentative procedures, including the distraction device will provide essential additional information for your readers. Further, explain your concept according the skeletal growth determination in young patients and time point for implant insertion, as this is not a standard concept in the daily practice.

A: The authors are grateful for the comment. The reasons for the extraction are now mentioned in the “Medical history and initial findings” section: “Additionally, in the area between teeth 46 and 47, a diffuse osteolysis confluent with a peri-coronar osteolysis around the retained 47 was visible.” The time point is mentioned in the “Enucleation of the KCOT with simultaneous bone grafting” section: “The cystectomy including the removal of the teeth 33, 45, 46 and 47 was performed in general anesthesia at the age of 12 years.” Furthermore, additional panoramic radiographs after bone grafting with the distractor (Figure 4) and the consolidation phase after distraction (Figure 5) were inserted into the manuscript.

The skeletal age of the patient was determined by a hand radiograph at the age of 15. As the method of skeletal age is routinely used by pediatricians, a specialist was consulted considering the estimation of maturation. As it is an individual estimation for a certain patient it is not
possible to establish a general concept. Furthermore, the mentioned issue has been discussed in
the discussion section: “The placement of dental implant in the adolescent is discussed
controversially. The fixed position during the growth of jaws, unpredictability and the
disarrangement of the dental arches have been considered as limitations (Moghadam 2014). On
the other hand, missing teeth might cause difficulties in speech and mastication as well as
impairment in the patient’s social life (Heuberer 2013). In the presented case, the cessation of
growth was estimated on the basis of a hand radiograph. This method of skeletal age assessment
is considered to be more reliable than the clinical age assessment regarding individual growth
development and degree of maturation (De Sanctis 2014). However, a wide variety has to be
respected. In the presented case, a decision was made to insert dental implants after the estimated
cessation of growth as implants placed in maturing adolescents have shown promising long
results (Heuberer 2013). However, long-term studies are currently missing.”

Discussion part. Please underline and discuss the problem of KCOT in young patients. Also
please discuss the pros and cons of your protocol of an early rehabilitation. The concept without
using autogenous bone, even in large bone defects in young patients. In the last part of the
discussion section, you recommend a radiographic check-up interval of three months during the
transitional dentition. However, this would mean, 4 times a year during age 6-16, in total 40
radiographs, which seems quite a high number. Please explain your concept, during transitional
dentition and afterwards.

A: The authors thank the reviewer for the comments. The discussion part has been revised
thoroughly: “Marsupialization of the KCOTs would have been another treatment option with a
comparable success rate to enucleation (Gupta 2015). A disadvantage over enucleation is the
considerable extended treatment period which was found to be around eleven months in a recent
study (Kubota 2013). The extended treatment time might be associated with a reduced quality of
life and is requiring a high level of compliance of the patient which might not be given in
children and adolescents. Furthermore, when multiple cysts are in situ a surgical removal of the
KCOTs might be the treatment of choice. However, in the presented case the patient did not want
the long-lasting treatment by marsupialization.

Furthermore, the reconstruction of large defects is challenging. Although autogenous bone is
considered as the “gold standard” in bone grafting the juvenile body offers limited amounts of
autogenous bone which is challenging to graft extended defects. Additionally, the use of
autogenous bone might be associated with donor site morbidity (von Arx 2006). Adolescents,
who are physically active might be limited in their daily life.”

“The placement of dental implant in the adolescent is discussed controversially. The fixed
position during the growth of jaws, unpredictability and the disarrangement of the dental arches
have been considered as limitations (Moghadam 2014). On the other hand, missing teeth might
cause difficulties in speech and mastication as well as impairment in the patient’s social life
(Heuberer 2013). In the presented case, the cessation of growth was estimated on the basis of a
hand radiograph. This method of skeletal age assessment is considered to be more reliable than
the clinical age assessment regarding individual growth development and degree of maturation
(De Sanctis 2014). However, a wide variety has to be respected. In the presented case, a decision
was made to insert dental implants after the estimated cessation of growth as implants placed in
maturing adolescents have shown promising long results (Heuberer 2013). However, long-term studies are currently missing.“

“As these recommendations would cause a considerable exposure to radiation in our case the radiographical check-ups in three-months intervals were performed until the eruption of the last permanent tooth. Subsequently, the interval was extended to six months. Thus, an early detection of translucent lesions in the regions of teeth 17 and 18 as well as 28 was possible. Subsequently, the extraction of 17 and the surgical removal of the wisdom tooth germs was indicated due to the development of another keratocystic odontogenic tumor. However, a balance between exposure of radiation and the risk of missing the recurrence of a cystic lesion has to be found.”

Furthermore, the radiographic follow-up scheme has been specified in the “Outcome and follow-up” section: “Regarding the histologically proven KCOTs a three-months radiological control interval was set up during the treatment period until the eruption of the last permanent tooth which was tooth 23 in the presented case.” and “Subsequently, the interval of radiographic examination has been extended to six months.”

Reviewer # 2

The reviewer has the following comments and questions:

Dear Authors:

Thank you for your interest in sharing your experience in the treatment of this patient. This manuscript is a good and interesting review of a long term and multidisciplinary treatment approach of a Gorlin-Goltz Syndrome case, presenting multiple jaw cysts. The patient was treated by cystectomy, allogenic bone grafting, distraction osteogenesis and dental implantation.

There are some general issues with the case presentation that need to be addressed:

- The writing style, grammar structure and punctuation of the manuscript might need improvement.

A: The manuscript has been revised in general considering the mentioned issues.

- The sequence of the data presented needs to be chronologically detailed.

A: The chronological sequence of the data has been presented more detailed in table 1.

Specific concerns:

1. The title is misleading since dental implants were inserted at the age of adolescence.
A: The authors thank the reviewer for this advice. The title of the manuscript has been changed into “Multidisciplinary oral rehabilitation of an adolescent suffering from juvenile Gorlin-Goltz syndrome – a case report” summarizing the main topic of the manuscript and considering the age of the patient.

2. Page 5, 23 - 24 section. After: "The following deciduous teeth were found to be in situ:", 83 was not mentioned and the next sentence refers to this tooth. Although, at the first orthopantomogram it cannot be observed.

A: The phrase that was criticized by the reviewer has been revised. The meaning was that the in the area where tooth 83 was located and now, tooth 43 is located. Now, the phrase is clarified and an additional phrase was inserted: “Furthermore, the permanent teeth 14, 16, 12-22, 26, 36, 32-43 and 46 were erupted. In the vestibular region of teeth 43 and 84 an indolent, solid, smooth-margined swelling with a diameter of 20 mm was obvious.”

3. Page 5, 34 - 36 section. The description of the radiographic lesions can be improved.

A: The orthopantomogram (OPT) showed a retention of the teeth 33 and 45 at the base of the mandible. In the peri-coronal area of both teeth enlarged radiolucencies with a clearly visible margin measuring about 32 x 28 mm in region 33 and 27 x 24 mm in region 45 were obvious. Additionally, in the area between teeth 46 and 47, a diffuse osteolysis confluent with a pericoronar osteolysis around the retained 47 was visible. Furthermore, the teeth 35, 34 and 44 were angulated disto-mesially and root resorptions at the teeth 73 and 85 were observed.

Additionally, the description of Figure 1 in the Legends section was extended: “Figure 1 – initial orthopantomogram (OPT) at the age of 11 years showing the extended pericoronar osteolyses of the teeth 33 and 45 which were retained at the base of the mandible. The adjacent teeth (32, 34, 44) seem to be dislocated by the cystic lesions. In the area between teeth 46 and 47, a diffuse osteolysis confluent with a pericoronar osteolysis around the retained 47 is obvious. Furthermore, root resorptions at the teeth 73 and 85 are visible.”

4. Page 6, 34 - 35 section. In the "Treatment plan" section, evaluate the goals of the orthodontic treatment. The patient was already eleven years old at the time of diagnosis, with a late mixed dentition stage.

A: The treatment plan section of the orthodontic was revised. It is now: “Orthodontic treatment to level the dental arches and to maintain space for implant supported oral rehabilitation in region of 33 and the right mandible.” In order to prevent mesial movement of the teeth, the orthodontic treatment was initiated directly postoperatively. This involved the fine adjustment of the dental arches with orthodontic movement of tooth 23 into the right position. Furthermore, the angulated teeth 32, 34 and 44 were erected. Thus, the cuspid space in region 33 was kept open and the remaining front teeth could be stabilized in order to allow insertion of dental implants.”
5. Page 6, 53-55 section. Did not mention the specific area described.

A: The entire paragraph has been revised in order to add the missing information: “The bony defect in region 33 measured about 32 x 28 mm and the defect in region 45 was approximately 27 x 24 mm. The lesion in the right mandible showed a length of approximately 60 mm and a height and width of approximately 20 mm.”

6. Page 7, 9-12 section. It can be observed at Figure 3 that teeth 45, 46 and 47 were extracted, without explaining the reasons or the procedure. The same happened for 17 tooth.

A: The entire paragraph has been revised in order to provide the mentioned missing information: “Based on the data obtained from the CBCT, a model was created. Subsequently, a CAD/CAM milled, allogenic bone block was produced for the defect resulting from the enucleation in the right mandible (Tutoplast® Spongiosa, Tutodent, Neunkirchen a. B., Germany). The customized bone block is shown in figure 2. The cystectomy including the removal of the teeth 33, 45, 46 and 47 was performed in general anesthesia at the age of 12 years. It was possible to achieve an enucleation in toto that histologically confirmed a KCOT by instantaneous section diagnosis. Simultaneously, the reconstruction of the defects in region 33 and 45 were performed using preformed allogenic spongiosa blocks (Tutoplast® Spongiosa, Tutodent, Neunkirchen a. B., Germany). In the right mandible, the customized spongiosa block was inserted (Figure 3).”

Furthermore, the findings and the procedures leading to the extraction of tooth 17 were included into the “Outcome and follow-up” section: “At the 6-months follow-up after insertion of the prosthetic restorations, OPT, lateral cephalogram and CBCT showed well osseointegrated implants without any sign of bone loss. No recurrence of the surgically removed KCOTs was observed. However, a new cystic lesion in the posterior part of the right sinus maxillaris was found. Tooth 17 and the germ of tooth were removed due to the close contact to the cystic lesion without complications. Histologic examination proofed another KCOT.”

7. Page 7, 19-22 section. The treatment of 23 was mentioned without previously describing what was observed in this area. Please, if possible broaden the reasons that led you to apply a different treatment for this tooth that was also in relation to a KCOT.

A: The authors revised the treatment and provided an explanatory statement for the different treatment of tooth 23: “As the KCOT was only located peri-coronally and tooth 23 was retained in a vertical position closed to eruption the preservation of 23 was intended. Thus, a bracket for forced orthodontic movement was attached to the tooth.”

8. Page 7, 32-37 section. Orthodontic treatment description needs improvement (e.g., mandibular and maxillary dental arches were leveled and aligned, traction of tooth 23 to its desired position was successfully achieved. The space between tooth 32 - 34 was maintained to perform prosthetic dental rehabilitation of missing tooth 33).
A: The authors revised the section mentioned in the reviewer’s comment: “In order to prevent mesial movement of the teeth in the left mandible, the orthodontic treatment was initiated directly postoperatively. This involved the fine adjustment of the dental arches with orthodontic movement of tooth 23 into the right position. Furthermore, the angulated teeth 32, 34 and 44 were erected. Thus, the cuspid space in region 33 was kept open and the remaining front teeth could be stabilized in order to allow insertion of dental implants in the right posterior mandible.”

9. The healing of allogenic bone graft and the morphology of right mandibular ridge before and after distraction osteogenesis are not well documented.

A: The authors added to the “Bone augmentation in the adolescent” section the information about the clinical healing: “The healing was uneventful without any dehiscence or signs of inflammation. Subsequently, the distraction phase was set up for 18 days followed by a consolidation phase of six months.” On page 8, section 35 – 38, the histological results of the healing are described: “The samples were embedded in paraffin and stained using hematoxylin eosin. The histological examination revealed vital spongy bone trabeculae along avital bone tissue with evidence of increased remodeling.”

Furthermore, in the “Bone augmentation in the adolescent” section the information of the height and width of the alveolar process in the right mandible was inserted: “Furthermore, a vertical deficit of about 8 mm in the right posterior mandible in regio 46 and 47 was obvious while the bone width was 12.9 mm. Only 9 mm of bone cranial of the mandibular canal could be measured providing an inappropriate crown to root relation.” and “Thus, a bone height of 15 mm cranial of the mandibular canal was achieved while the bone width decreased slightly to 11.5 mm which, however, could considered sufficient for the insertion of dental implants.”

10. Page 9. At the first paragraph of the "Outcome and follow-up period" it is stated that a radiolucency between 46 and 47 was noted during the follow-up, but no treatment for that was described. Actually, on the original orthopantomogram taken at age 11 (Figure 1), a radiolucent lesion distal to 46, causing displacement of the 47 tooth germ was already noticeable.

A: The authors are grateful for this comment. The section has been revised and the treatment has been included in detail in the treatment plan section. The following sentence has been added to the section of the Medical history and initial findings sections: “Additionally, in the area between teeth 46 and 47, a diffuse osteolysis confluent with a peri-coronar osteolysis around the retained 47 was visible.”

11. Page 10. KOTC instead of KCOT was used.

A: The authors thank the reviewer for this advice. The mistake has been revised.

12. Page 10, 32-33 section. Refers to a case without mentioning the author.
A: The author of the case report was added to the phrase: “In the case of a 26-year old male patient the surgical therapy included the decompression and enucleation of the KCOT and the surgical removal of the impacted tooth [34]. During the follow-up period of 31 months, Brkic et al. observed no sign of recurrence and the fixed bridge borne on two implants was functional.”

13. Page 11, section 57. In "Discussion", it is stated that lesions in the regions of 17, 18 and 27, 28 were detected and 17, 27 were extracted. The treatment is not mentioned in "Case presentation". Furthermore, on the orthopantomogram taken at age 20 (Figure 5) 27 is still present.

A: The authors are grateful to the reviewer for this advice. The sentences have been revised: “Thus, an early detection of translucent lesions in the regions of teeth 17 and 18 as well as 28 was possible. Subsequently, the extraction of 17 and the surgical removal of the wisdom tooth germs was indicated due to the development of another keratocystic odontogenic tumor.”

In the “Outcome and Follow-up” section the following statement was included: “At the 6-months follow-up after insertion of the prosthetic restorations, OPT, lateral cephalogram and CBCT showed well osseointegrated implants without any sign of bone loss. No recurrence of the surgically removed KCOTs was observed. However, a new cystic lesion in the posterior part of the right sinus maxillaris was found. Tooth 17 and the germ of tooth were removed due to the close contact to the cystic lesion without complications. Histologic examination proofed another KCOT. At the 12-months follow-up, lesion in the basal part of the left sinus maxillaris was observed. As the radiographic control showed a rapid progression of the lesion in the left sinus, it was surgically removed together with the germ of 28 in general anesthesia.”

14. Page 12. In "Conclusion", the statement of the occurrence of basal cell carcinomas is true but is the first time it is addressed on the manuscript, might not be included as a conclusion for this specific case report.

A: The authors thank the reviewer for this comment: However, on page 3, section 8-13 it is stated that the Gorlin-Goltz syndrome is characterized by “KeratoCystic Odontogenic Tumors (KCOT) in the jaws, multiple basal cell carcinomas and skeletal abnormalities [2–7]”. Furthermore, on page 6, section 23-26, it is mentioned that a follow-up considering “physical screenings focusing on dermal and ophthalmic anomalies on a regular three-month interval” is recommendable. On one hand, the dermal areas are easily accessible for check-ups, on the other hand the development and growths of basal cell carcinomas might have an impact on the quality of life especially for young patients. A frequent dermal screening might be helpful in avoiding the growths of extended basal cell carcinomas and thus, avoiding extended scars which might hamper the appearance of the person. That is why the authors would like to include this statement as a conclusion in the case report.

15. It is important to include why the authors didn't consider cyst decompression/marsupialization as a treatment option. Clinical experiences have demonstrated
that cyst decompression/marsupialization may preserve teeth and bone in the management of odontogenic keratocysts, whether they are syndrome-associated or sporadic.

A: The authors added a paragraph discussing the pros and cons of marsupialization of the cysts: “Marsupialization of the KCOTs would have been another treatment option with a comparable success rate to enucleation (Gupta 2015). A disadvantage over enucleation is the considerable extended treatment period which was found to be around eleven months in a recent study (Kubota 2013). The extended treatment time might be associated with a reduced quality of life and is requiring a high level of compliance of the patient which might not be given in children and adolescents. Furthermore, when multiple cysts are in situ a surgical removal of the KCOTs might be the treatment of choice. However, in the presented case the patient did not want the longer treatment by marsupialization.”

Furthermore, the following section was added to the treatment plan: “In order to find a satisfying treatment for the patient the options of marsupialization and enucleation of the cystic lesions were discussed with the patient and his family. Due to the long treatment period associated with the marsupialization enucleation of the lesions with simultaneous augmentation of the resulting defects was preferred.”

I hope that the suggestions mentioned can be helpful for the improvement of the case report.