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USP6 Translocation in Giant Cell Granulomas of the Jaws

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INTRODUCTION

- Central giant cell granulomas (CGCG) account for 7% of all benign tumors of the jaw while peripheral giant cell granulomas (PGCG) occur on the gingiva (Table 1).
- The underlying pathophysiology of CGCG and PGCG is not known. Therefore there are studies attempting to identify biomarkers to increase understanding the pathogenesis of CGCG and PGCG.
- Some authors consider CGCG in jaw bones similar to giant cell tumors of long bones while others believe them to be reactive or non-neoplastic lesions.
- Recurrence of these lesions following conservative treatment is attributed to matrix metalloproteinases, namely MMP9. Recent studies have shown an increase in levels of MMP 9 in central and peripheral giant cell granulomas as in aneurysmal bone cysts (ABC).
- De-ubiquitinating enzymes play an important role in cellular processes, though their precise role in normal physiology is not fully understood. USP6 is the first de-ubiquitinating enzyme recognized as an oncogene.
- Recently studies have described the USP6 translocation in CGCG as transforming this lesion to a neoplasm. This retrospective study analyzed two cases of CGCG and one PGCG for the USP6 translocation.

MATERIALS & METHODS

Studied representative samples from two cases of recurrent CGCG and one case of recurrent PGCG cytogenetically; each case exhibited typical microscopic and radiographic features of CGCG and PGCG. The clinical data for three patients are summarized in Table 2.

Fluorescence in situ hybridization (FISH) study:

- Deparaffinized paraffin-embedded 4 µm tissue sections in xylene, dehydrated in 100% ethanol, and treated with 100mmol/L Tris and 50mmol/L EDTA (pH7.0) for 15 minutes at 93°C.
- Rinsed tissue sections once in PBS and protein digested with Digest All-3.
- Sequentially dehydrated these slides in alcohol (70%, 85%, 95% and 100%) and air dried for an hour at room temperature.
- Denaturated tissue sections at 75°C for 2 minutes and carried out BAC probe hybridization overnight in a humidified chamber at 37°C.
- Washed tissue sections in 0.5 x SSC for 5 minutes at 73°C and treated with CAS block for 10 minutes.
- Performed USP6 probe detection using FITC-anti-digoxigenin (1:500) and Alexa Fluor 594-streptavidin (1:500) (molecular probe, Eugene, OR) for 30 minutes.
- Mounted slides in Vectashield mounting medium.
- CGCG and PGCG scored positive for gene arrangement if more than 5%of cells showed splitting apart of the FISH probes.

RESULTS

Figure 1. USP6 Breakapart Probe Control

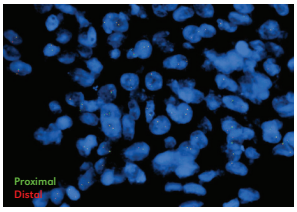
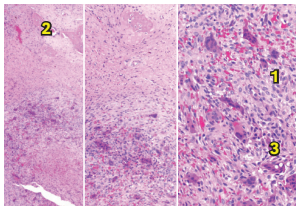


Figure 2. Photomicrograph Showing Central Giant Cell Granuloma



1) bland spindle cells, 2) reactive new bone
3) multinucleated giant cells

Figure 3. Case 1. Central Giant Cell Granuloma Showing No Rearrangement of USP6 Breakapart Probe

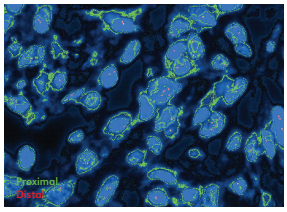


Figure 4. Case 2: Central Giant Cell Granuloma Showing No Rearrangement of USP6 Breakapart Probe

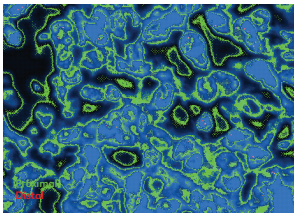
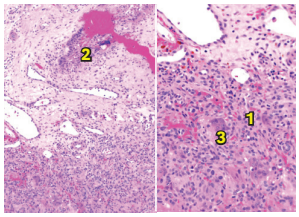


Figure 5. Photomicrograph Showing Peripheral Giant Cell Granuloma



1) bland spindle cells, 2) surface epithelium,
3) multinucleated giant cells

Figure 6. Case 3: Peripheral Giant Cell Granuloma Showing No Rearrangement of USP6 Breakapart Probe

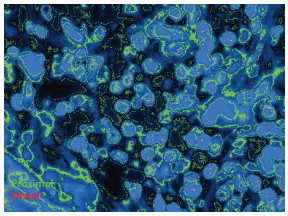


Table 1. Characteristic Clinical Features of CGCG & PGCG

	CGCG		PGCG
Peak Prevalence	60% occur before 30 years		31-41 years
Gender Prevalence	Females		Females
Location	Anterior Mandible		Mandibular Gingiva
Clinical Signs & Symptoms	Aggressive Symptomatic: Pain Rapid Growth Cortical Perforation	Non-aggressive Asymptomatic: Slow Growth	Presents as red/red=blue, sessile/pedunculated nodular mass
Radiographic Findings	Unilocular or multilocular radiolucencies with noncorticated margins		None, may see some "cupping" resorption of underlying alveolar bone
Recurrence	15-20%		10%

Table 2. Clinical Data of Three Patients

Case	Location	Gender	Age (years)	Microscopic Diagnosis
1	Anterior Maxilla (Apical to #9-10)	Male	18	Central giant cell granuloma
2	Anterior Mandible (#24)	Female	37	Central giant cell granuloma
3	Anterior Mandible (Gingiva #23-24)	Female	57	Peripheral giant cell granuloma

DISCUSSION

- WHO has defined CGCG as an intraosseous lesion consisting of cellular fibrous tissue containing multiple foci of hemorrhage, aggregations of multinucleated giant cells and occasional trabeculae of woven bone.
- CGCG can present as unilocular or multilocular, radiolucent bone lesions while PGCG occurs as a gingival lesion.
- In this pilot study, recurrent CGCG and PGCG failed to demonstrate a rearrangement of USP6 genes. This lack of USP6 rearrangement suggests a reactive rather than a neoplastic pathogenesis.
- Future studies to understand the pathogenesis of these poorly understood lesions is suggested to confirm this hypothesis.

CONCLUSION

The results of this pilot study imply that CGCG and PGCG are reactive lesions with little or no neoplastic potential and may be managed conservatively.