Immunohistochemical expression of stem cell markers OCT-4 and SOX-2 in giant cell tumor, central giant cell granuloma, and peripheral giant cell granuloma

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Objectives. This study aimed to evaluate and compare the immunohistochemical expression of OCT-4 and SOX-2 and to determine their use in differentiating giant cell tumor (GCT) from central giant cell granuloma (CGCG) and peripheral giant cell granuloma (PGCG).

Study Design. Formalin-fixed, paraffin-embedded tissue blocks of 10 histopathologically diagnosed cases of GCT, CGCG, or PGCG were examined for anti−OCT-4 and anti−SOX-2 antibodies. Nuclear staining of stromal mononuclear cells and multinucleated giant cells was considered positive for OCT-4 and SOX-2 expression.

Results. Nuclear immunoexpression of OCT-4 in stromal mononuclear cells was observed in 80% (8 of 10) of GCT cases, whereas none of the CGCG and PGCG cases showed OCT-4 immunoreactivity. SOX-2 immunoreactivity was negative in GCT, CGCG, and PGCG.

Conclusions. OCT-4 immunopositivity in GCT can be used as a cancer stem cell marker to differentiate GCT from CGCG and PGCG. The presence of OCT-4 in GCT versus its complete absence in CGCG and PGCG suggests that these three conditions are separate entities. The absence of stem cell marker OCT-4 and SOX-2 raises questions regarding their role in the pathogenesis of CGCG and PGCG. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:78−84)

Giant cell lesions of the maxillofacial skeleton and other bones are a controversial topic, and uncertainty still exists regarding their basic pathology and biologic behavior.[1] Giant cell granulomas occurring within the jaws and those on the gingival or edentulous alveolar processes are termed *central giant cell granuloma* (CGCG) and *peripheral giant cell granuloma* (PGCG).[2] CGCG is an uncommon, nonneoplastic, slow-growing, locally aggressive osteolytic lesion, with a distinct clinical behavior.[3] They are common in the second and third decades of life, occur in anterior part of mandible, show female predilection, and radiographically present as a unilocular or multilocular radiolucent lesion with defined outlines but noncortical margins.[4] PGCG is a relatively common lesion that is thought to arise peripherally in the periodontal ligament and the mucoperiosteum of the alveolar ridge in reaction to local stimulatory factors and runs an indolent course.[5] Radiographically, PGCG characteristically exhibits superficial erosion of bone with pathognomonic peripheral cuffing.[6]

Giant cell tumor (GCT) was first described by Sir Astley Cooper in 1818, and later, Bloodgood coined the term *GCT* in 1912. In 1940, Jaffe and Lichtenstein further defined its clincoradiohistopathologic identity.[7] GCT of bone is a benign, locally aggressive osteolytic neoplasm with a high recurrence rate and typically affects the epiphyseal or metaphyseal region of the long bones, most commonly involving the distal femur, proximal tibia, distal radius, and proximal humerus.[8] It accounts for 4% to 5% of all primary bone tumors and 13% to 20% of all benign bone tumors, with a peak incidence in the third and fourth decades of life, and exhibits a slight female predilection. GCT can occasionally metastasize to the lungs, but malignant transformation into sarcoma is rare.[9]

The typical radiographic appearance of GCT is that of an entirely lytic expansile lesion in the epiphysis, usually without peripheral bone sclerosis or periosteal reaction.[10] Before 1953, researchers generally did not

Statement of Clinical Relevance

On the basis of our findings, OCT-4 immunoexpression can be used as a novel stem cell marker in differentiating giant cell tumor (GCT) from central giant cell granuloma (CGCG) and peripheral giant cell granuloma (PGCG). The findings of this study strengthen the view point that GCT is a separate entity from CGCG and PGCG and indicate that there may be a stem cell−like subpopulation in the stromal mononuclear cells of GCT and can provide a biologic basis for a new, more specific therapeutic approach.

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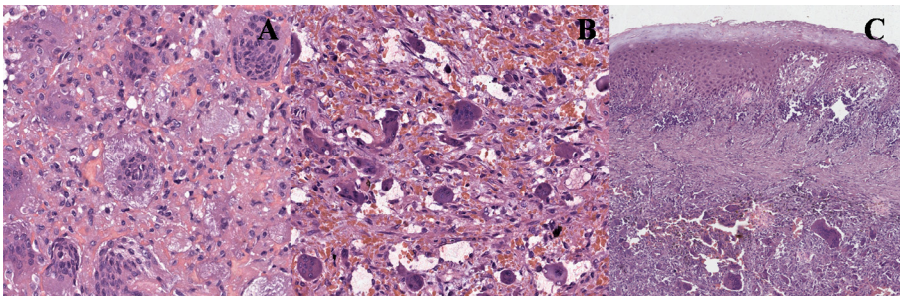

Fig. 1. **A,** Photomicrographs (hematoxylin and eosin [H&E] stain) showing histologic features in GCT (original magnification ×100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05799.* **B,** Photomicrograph ((H&E stain) showing histologic features in CGCG (original magnification ×100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05812.* **C,** Photomicrograph (H&E stain) showing histologic features in PGCG (original magnification ×100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05798.*

distinguish between giant cell lesions of the jaws and GCT of the long bone. Jaffe introduced the term "giant cell reparative granuloma" of the jaws and was the first to distinguish this lesion from GCT.[2] Current nomenclature omits the word *reparative* because of the locally destructive, invasive, and enlarging nature of the lesion.[2,11] Histologically CGCG, PGCG, and GCT share common features, with multinucleated giant cells present in a background of ovoid to spindle-shaped mesenchymal cells within a fibrous stroma.[4,12] Some histologic differences reported to be more common in CGCG and PGCG compared with GCT include the presence of large areas of fibrosis, hemorrhage, hemosiderin deposits, and osteoid[4,12,13] (Figures 1A, 1B, and 1C). Because of the considerable overlap of these features, these differences have not been proven to be diagnostically reliable.[1] Whitaker and Waldron reported that CGCG of the jaws and GCT of the long bones could represent the development of a single pathologic process that may be influenced by the patient's age, tumor location, and other unknown factors.[14]

Cancer stem cells (CSCs) have been described as a small subset of cells within a tumor, endowed with features similar to those of normal stem cells. These features include extensive proliferation, self-renewal, anchorage-independent survival, and differentiation into more mature progeny.[15] CSCs are recognized as the key cells responsible for tumorigenesis and recurrence and express stem cell marker genes.[16-19] OCT-4 is a class V, Pit-1, OCT 4, Unc-86 (POU) domain family of octamer-binding transcription factors, located on chromosome 6 in humans. OCT-4 plays a critical role in the development and self-renewal of embryonic stem cells and has been linked to oncogenic processes.[20,21] Sex-determining region Y-box2 [SRY] (SOX- 2) is a transcription factor involved in the maintenance of embryonic stem cell (ESC) pluripotency, multiple developmental processes, and the differential potential of stem cells.[22] SOX-2 has also been found to play a role in tumorigenesis of cancers, including squamous cell carcinoma, gastric cancer, glioblastoma, colorectal cancer, and lung and breast cancers.[22,23]

Previous studies have used OCT-4 and SOX-2 in GCT and in reactive lesions, such as pyogenic granuloma.[15,24-26] An extensive search of the literature revealed no studies on the expression of these markers

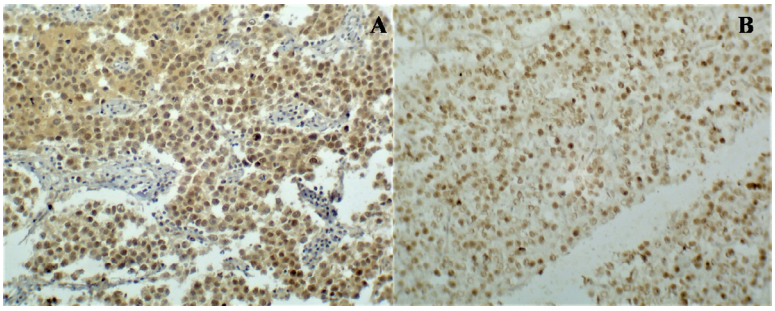

Fig. 2. **A,** Photomicrograph showing immunoexpression of OCT-4 in seminoma (positive control) (immunohistochemistry [IHC]; original magnification ×100) *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05802.* **B,** Photomicrograph showing immunoexpression of SOX-2 in Glioma (Positive control) (IHC, original magnification ×100) *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05808.*

in CGCG and PGCG. The present study aimed to determine OCT-4 and SOX-2 immunoreactivity in GCT, CGCG, and PGCG and to understand their use in differentiating among these 3 entities.

MATERIALS AND METHODS

We retrieved 10 histopathologically diagnosed cases of GCT, CGCG, and PGCG from the archives of the Department of Oral Pathology and Microbiology and the Department of General Pathology of the Nair Hospital Dental College (Mumbai, India). The study was approved by the Institutional Ethics Committee (EC-107/OPATH-10 ND/2018). The study design was in accordance with the principles of the Declaration of Helsinki and consistent with the guidelines of Good Clinical Practice as given by the International Conference on Harmonization (ICH-GCP).[27] Giant cell lesions associated with any other pathology were excluded.

Immunohistochemical staining

Five-μm sections were cut from formalin-fixed, paraffin-embedded tissue blocks and mounted on SuperFrost slides. Immunohistochemical (IHC) staining was carried out by using the polymer labeling technique. The sections were dewaxed and washed, and antigen retrieval was carried out in the PT Link module with 1-mM ethylenediaminetetraacetic acid solution (pH 9) for 20 minutes. Endogenous peroxidase was blocked by using 3% hydrogen peroxide in methanol at room

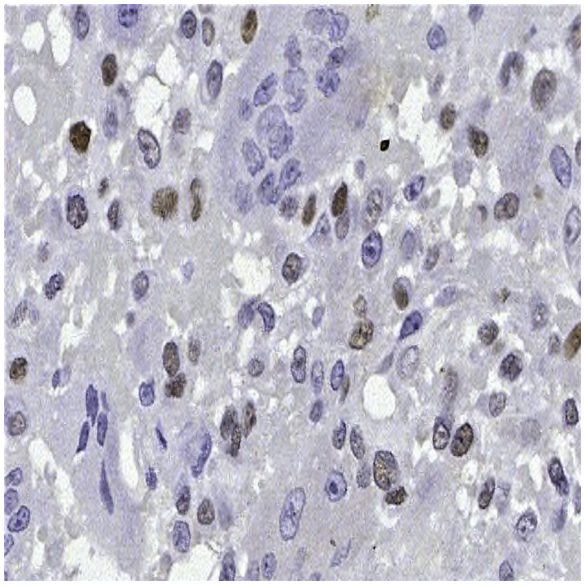

Fig. 3. Photomicrograph showing positive immunoexpression of OCT-4 in mononuclear stromal cells of GCT (immunohistochemistry [IHC]; original magnification ×400) *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05807.*

Table I. Comparison of OCT-4 immunoexpression in GCT, CGCG, and PGCG

Lesions	*Total No. of cases*	*OCT-4–positive cases % (n)*	*Intensity of staining score (n)*			*Proportion of cell staining score % (n)*				*Combined score (2–7 points)*		
			1+	*2+*	*3+*	*1%–5%*	*6%–25%*	*26%–50%*	*> 50%*	*2 & 3 Low*	*4 & 5 Intermediate*	*6 & 7 High*
GCT	10	80 (8)	70 (7)	10 (1)	0	70 (7)	10 (1)	0	0	7	1	0
CGCG	10	0	0	0	0	0	0	0	0	0	0	0
PGCG	10	0	0	0	0	0	0	0	0	0	0	0

CGCG, central giant cell granuloma; *GCT*, giant cell tumor; *PGCG*, peripheral giant cell granuloma.

temperature for 10 minutes. Immunostaining was carried out on the Dako autostainer (Dako Agilent Technologies, Santa Clara, CA). Sections were washed with phosphate-buffered saline (PBS) briefly and incubated with primary antibody against OCT-4 (Clone: MRQ-10 mouse monoclonal antibody; Cell Marque, Rocklin, CA) and SOX-2 (Clone: EP103 mouse monoclonal antibody; PathnSitu Biotechnologies, Rocklin, CA) for 60 minutes. Sections were washed with PBS and incubated with the EnVision polymer (Dako Agilent Technologies, Santa Clara, CA) for 30 minutes and were washed again with PBS. Diaminobenzidine was used as the chromogen in hydrogen peroxide for 10 minutes and were then counterstained with the Mayer hematoxylin and mounted. Sections of seminoma and glioma were used as positive controls for OCT-4 and SOX-2, respectively (Figures 2A and 2B). Exclusion of the primary antibody served as the negative control.

Immunohistochemical analysis

The IHC stained slides were examined under the research microscope (Axiolab, Carl Zeiss, Germany) with photomicrography attachment (Moticam 1000). OCT-4 and SOX-2 antibodies were considered positive when nuclei of single or more lesional stromal mononuclear and giant cells stained brown. The positive staining intensity and the proportion of cells staining positively were scored with a slight modification of the criteria given by Reiner et al. and Barnes et al.[28] The intensity was scored by evaluating the average intensity of the entire tissue section as 0 (no staining); 1 (visible at high-power magnification, ×400); 2 (visible at low-power magnification, ×100); and 3 (visible at scanner view, ×40). The total proportion of cells staining positively at any intensity was scored by screening 5 fields per tissue section at random as 0 (no cell staining); 1 (1%−5% stained cells); 2 (6%−25% stained cells); 3 (26%−50% stained cells); and 4 (> 50% stained cells). "Quick score" was calculated by combining the intensity and proportion score:

"Quick score" = intensity score + proportion score

In this scoring method, each tumor with a quick score of 2 or 3 points was consider as low, 4 and 5 points as intermediate, and 6 and 7 points as high for OCT-4− and SOX-2−positive immunoexpression.

RESULTS

OCT-4−positive immunoreactivity was seen in the nuclei of the stromal mononuclear cells of GCT (80%; 8 of 10 cases) with a combined score of 2 and 3 but was negative in the multinucleated giant cells (Figure 3; Table I). In CGCG and PGCG, OCT-4 was found to be negative in both stromal mononuclear cells and multinucleated giant cells (Figures 4A and 4B). In contrast, negative immunoreactivity was observed for SOX-2 in both stromal mononuclear cells and multinucleated giant cells in GCT, CGCG, and PGCG (Table II; Figures 5, 6A and 6B).

DISCUSSION

CSCs are a subpopulation of stemlike cells within tumors and exhibit characteristics of both stem cells and cancer cells. They are characterized by the same unique properties of ESCs, such as self-renewal ability and multilineage differentiation, leading to tumor development and progression. CSCs play a potential role in tumor aggressiveness, treatment resistance, and tumor recurrence (relapse), and metastasis.[16]

The core transcription factors that control "stemness" in ESCs include OCT-4, SOX-2, NANOG, Myc, and Klf4. The combination of these factors has been shown to successfully reprogram differentiated somatic cells into pluripotent stem cells.[22] There is substantial evidence that CSCs express these specific

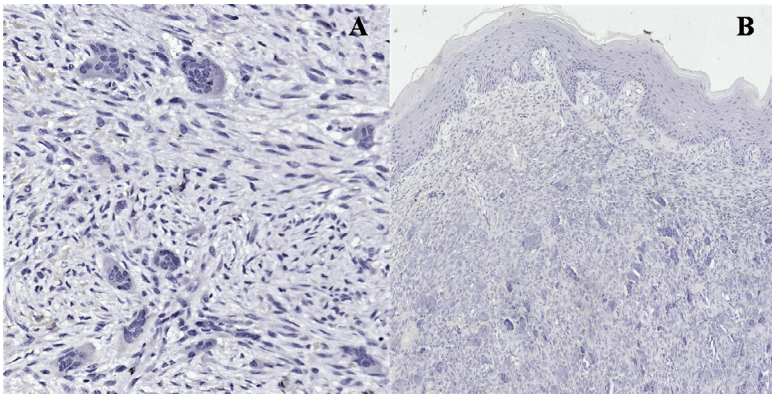

Fig. 4. **A,** Photomicrograph showing negative immunoexpression of OCT-4 in CGCG (immunohistochemistry [IHC]; original magnification ×100) *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05800.* **B,** Photomicrograph showing negative immunoexpression of OCT-4 in PGCG (IHC, original magnification ×100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05803.*

Table II. Comparison of SOX-2 immunoexpression in GCT, CGCG, and PGCG

Lesions	*Total No. of cases*	*SOX-2−positive cases % (n)*	*Intensity of staining score (n)*			*Proportion of cell staining score % (n)*			*Combined score (2−7 points)*		
			1+	*2+*	*3+*	*1%−5%*	*6%−25%*	*26%−50%*	*> 50%*	*2 & 3 Low*	*4 & 5 Intermediate*	*6 & 7 High*
GCT	10	0	0	0	0	0	0	0	0	0	0	0
CGCG	10	0	0	0	0	0	0	0	0	0	0	0
PGCG	10	0	0	0	0	0	0	0	0	0	0	0

CGCG, central giant cell granuloma; *GCT*, giant cell tumor; *PGCG*, peripheral giant cell granuloma.

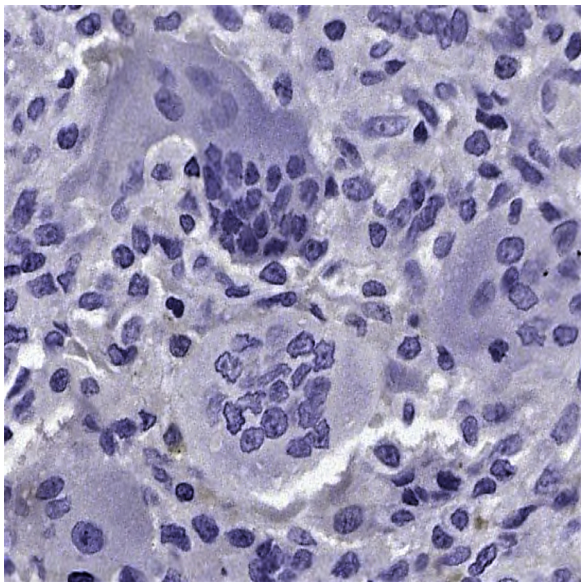

Fig. 5. Photomicrograph showing negative immunoexpression expression of SOX-2 in GCT (immunohistochemistry [IHC]; original magnification ×400) *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05809.*

markers and that their activity contributes to the oncogenic properties.[22,23] There are 20 SOX proteins. Three genes, *SOX-1, SOX-2*, and *SOX-3*, show similarity to the Sry (sex−determining region of chromosome Y) protein, have a high-mobility group (HMG) DNA-binding domain, and are localized in nucleus and cytoplasm. They are widely expressed in embryonic as well as adult tissues and require other transcription factors, such as partner proteins, for control of their activities. SOX-2 heterodimerizes with OCT-4, and together, they bind to a consensus DNA sequence that is present in the target genes.[29]

OCT-4 is known to have 2 isoforms, OCT-4A and OCT-4B. OCT-4A is observed in the nucleus and OCT-4B is observed in the cytoplasm. Because OCT-4 is a transcriptional regulator, the active form of OCT4 is always located in the nucleus.[30]

There is an age-old controversy regarding GCT, CGCG and PGCG being separate entities or variants of the same disease found at different locations. Histopathologically, GCT, CGCG, and PGCG show the presence of multinucleated giant cells and mononuclear stromal cells (see Figures 1A, 1B, and 1C). Although GCT is known for the osteoclast-like giant cells, the mononuclear spindle-shaped stromal cells are believed to be the neoplastic element of GCT.[24] These cells constitute the proliferative population of GCT, can stimulate formation of giant cells, and are responsible for the aggressiveness of the lesion. Recently, CSCs, such as Stro-$^{1+}$, ^{c}-Met^{+}, and ALCAM^{+}, have

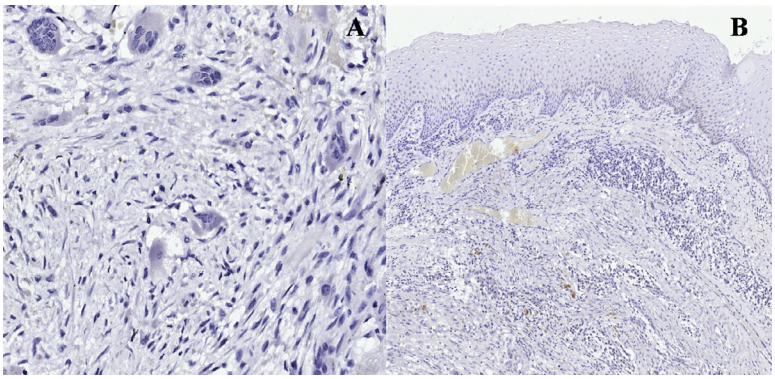

Fig. 6. **A,** Photomicrograph showing negative immunoexpression expression of SOX-2 in CGCG (immunohistochemistry [IHC]; original magnification ×100) *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05804.* **B,** Photomicrograph showing negative immunoexpression expression of SOX-2 in PGCG (IHC, original magnification ×100) *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05806.*

been studied and found to be positive in the stromal cells of GCT.[15,24,25] Therefore, our study was designed to identify the CSC-associated genes *SOX-2* and *OCT-4* in GCT, CGCG, and PGCG; and, to date, no such work has been done.

Lan et al. demonstrated that the Stro-1^+ stromal cells in GCT possess stem cell–like biologic and molecular phenotypes, indicating that they are CSCs of GCT. Those authors found significant expression of the cell surface markers CD44 and CD117 and the stem cell–associated genes *OCT3/4, NANOG*, and *ABCG2*, in the Stro-1^+ subpopulation.[15] Similarly, Liu et al. further elucidated the existence of a stem cell population in GCT by showing positive expression of *OCT-4, NANOG*, and *SOX-2* in the stromal cells of GCT.[25] Zhou et al. also found *OCT-4, NANOG, SOX-2*, and *BMI* expression within the mononuclear stromal cells of GCT and concluded that they may represent potential therapeutic targets in aggressive and recurrent GCT.[24]

In the present study, we observed positive expression of OCT-4 in the nuclei of the stromal mononuclear cells in GCT (80%; 8 of 10), in accordance with the findings observed by Lan et al., Liu et al. and Zhou et al.[14,23,24] We found negative SOX-2 immunoreactivity in GCT, which was in contrast to the findings by Liu et al.[24] and Zhou et al.,[23] who demonstrated positive immunoreactivity for SOX-2 in the stromal cells of GCT.[14,23,24] The presence of OCT-4 and the absence of SOX-2 in GCT in our study could be attributed to the SOX-2–independent OCT-4 activation pathway; this needs to be further investigated in future studies. In CGCG and PGCG, we found negative immunoexpression of OCT-4 and SOX-2.

As shown by our findings on OCT-4 immunostaining, CSCs may be present in GCT, and this can provide a biologic basis for a new therapeutic approach. OCT-4 immunopositivity in GCT and its negative immunoexpression in all cases of CGCG and PGCG suggest that the pathogenesis of GCT is different from that of CGCG and PGCG. It also suggests that GCT is a neoplastic entity separate from CGCG and PGCG.

CONCLUSIONS

The present study demonstrated the existence of a CSC-like subpopulation only within the stromal cells of GCT of the long bone, but not in CGCG and PGCG, thus questioning the role of CSCs in the pathogenesis of CGCG and PGCG. This finding supports the view point of Abrams et al.[30] and Jaff et al.[2] that CGCG and GCT are distinct lesions and not a continuum of single disease process. Thus, OCT-4 immunostaining cannot be used in differentiating CGCG from PGCG. Further studies with larger sample sizes and extensive molecular research will be beneficial to clarify the pathogenesis and nature of these giant cell lesions.

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