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Giant cell granuloma of the jawbones – a proliferative vascular lesion? Immunohistochemical study with vascular endothelial growth factor and basic fibroblast growth factor

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AIM: To estimate the angiogenic activity in central giant cell granuloma (CGCG) by immunohistochemical stains for vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). VEGF and bFGF immunoreactivity of the lesional mononuclear (MC) and giant (GC) cells was also investigated.

METHOD: The study consisted of 41 cases of CGCG. Vascularity was quantified by microvascular volume (MVV) as determined by point counting. In five cases of CGCG, regions at the surrounding border, which demonstrated reactive vascular-rich inflammatory areas, served as control. Immunoreactivity of the MC and GC was assessed as the percentage of VEGF- and bFGF-positive cells from the total number of the respective cell type.

RESULTS: Within CGCG lesions the extent of angiogenesis was low; MVV did not exceed 5% for either VEGF (88% of lesions) or bFGF (78% of lesions). The mean MVV of VEGF- and bFGF-positive blood vessels was 2.9% ± 2.4% and 3.46% ± 2.35%, respectively, significantly lower than in the control areas (27.5% ± 7.3% and 28.08% ± 5.5%, respectively) ($P = 0.043$). VEGF-positive and bFGF-positive MC and GC were found in nearly all lesions and in less than half of the lesions, respectively.

CONCLUSION: The low mean MVV of VEGF- and bFGF-positive blood vessels implies low angiogenic activity, which does not support the designation of CGCG as a true proliferative vascular lesion. MC and GC immunoreactivity for the angiogenic factors is assumed to play an important role in the osteoclastogenesis process, thus contributing to additional growth of the CGCG lesions.

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Introduction

Central giant cell granuloma (CGCG) is a non-odontogenic lesion that comprises approximately 10% of all benign lesions of the jaws. More than 60% of all cases occur before the age of 30 years and has been found in children as young as 2 years old (1). Histologically, these lesions are characterized by the presence of numerous multinucleated giant cells (GC) embedded in a fibrocellular stroma often found adjacent to blood vessel walls. Foci of hemorrhage with hemosiderin pigment and newly formed osteoid or bone are occasionally observed. The nature of GC is still uncertain, but has been considered as phagocytes, foreign body cells, or osteoclasts (2). The relationship of GC with stromal mononuclear cells (MC) has not been fully elucidated. Recently, it has been suggested that stromal MC may be responsible for the formation of multinucleated GC or may represent their precursors (2, 3). Furthermore, GC may simply represent a reactive component of the lesion and may be present only in response to an unknown stimulus from the stroma (4).

The histogenesis of CGCG of the jawbones remains controversial, as speculations are still debated regarding the possibility that it represents a reactive, an inflammatory, an infective, or a neoplastic process (4). Another theory is the vascular hypothesis that suggests that CGCG belongs to the spectrum of mesenchymal proliferative vascular primary jaw lesions (5–7).

Angiogenesis is a phenomenon modulated by several cytokines and growth factors. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are the most potent inducers of angiogenesis and have a synergistic effect (8). VEGF, a soluble molecule that functions in an autocrine and paracrine manner, guides vascular development, serves as a highly specific mitogen for vascular endothelial cells, markedly induces vascular permeability and acts as a survival factor for newly formed blood vessels (8–11). It is produced and released from activated monocytes and macrophages (12, 13). Recently, vascular endothelial cells have been shown to be a major source of VEGF

(11). bFGF, a prototype member of a family of 13 structurally related heparin-binding growth factors with the ability to modulate cell functions in a paracrine and autocrine manner (8, 14, 15), is expressed ubiquitously in cells of mesodermal and neuroectodermal origin and in a variety of tumor cells. bFGF, *in vivo*, is a potent inducer of angiogenesis with pleiotropic effects on development and differentiation in different organs (8, 15).

The purpose of this study was to assess angiogenesis as reflected by VEGF and bFGF expression by the microvascularity of a large series of CGCG of the jawbones and to compare it to reactive vascular-rich inflammatory areas at the periphery of the lesions. The immunoreactivity of lesional MC and GC to VEGF and bFGF was also investigated.

Material and methods

Study cases

For the study, 41 formalin-fixed, paraffin-embedded blocks of CGCG were retrieved from the archives of the Department of Oral Pathology, School of Dental Medicine, Tel Aviv University. Table 1 summarizes the demographic data of the cases. There were 23 women and 18 men, ranging in age from 2 to 86 years (mean 38.6 years). Lesions were located in the maxilla (19 cases) and in the mandible (22 cases). All demonstrated radiographic evidence of an intrabony lesion. Hyperparathyroidism was suspected in one case and therefore excluded. Patients did not receive any therapeutic agent for treatment of CGCG.

Staining procedure

Sections (3 μ thick) were mounted on positive-charged microscope slides (Optiplus^{TM}; Biogenex, San Ramon, CA, USA). After dewaxing in xylene, sections were dehydrated in ethanol, rinsed in distilled water, placed in 3% H_2O_2 for 10 min and rinsed in distilled water for 10 min. Slides were exposed to primary anti-VEGF polyclonal anti-rabbit antibody, *sc*-152 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), dilution 1:100 for 20 min in a microwave in EDTA solution, pH = 8. For bFGF detection, polyclonal anti-rabbit antibody was used, *sc*-79 (Santa Cruz Biotechnology, Inc.), dilution 1:100 for 15 min in a microwave in EDTA solution, pH = 8. For antibody detection, universal immune peroxidase polymer anti-mouse rabbit Histofine^{R} (Multi) kit was used (Nichirei, Tokyo, Japan). Sections were rinsed in PBS for 10 min, reacted with AEC substrate-chromagen kit (Zymed, San Francisco, CA, USA), rinsed in distilled water for 2 min, counterstained in Mayer's hematoxylin (Pioneer Research Chemicals, Colchester, UK), and covered with glycerol vinyl alcohol (GVA) mounting medium (Zymed, San Francisco, CA, USA).

Staining evaluation

Quantification of VEGF-positive blood vessels within CGCG

A modified stereological method of measuring microvascular volume (MVV), determined by point counting, was carried out using an eyepiece graticule containing 100 squares (Olympus, Tokyo, Japan) at ×200 magnification (16, 17). Briefly, systematic sampling was used to select 10 fields across each section. The top peripheral border of the graticule was placed at the top left corner of the section and scanned. When a graticule-square junction between a vertical and horizontal line coincided with either VEGF positively stained endothelial cells of blood vessel walls or their lumina, it was considered as one count. Areas of hemorrhage were not included in the counting. After completing the enumeration of one field (121 points), the grid was moved horizontally in a precise distance beyond the scanned field by reference to the peripheral borders of the grid itself. Point counting proceeded onto a new field. Repetition was continued until completion of the first upper horizontal transverse. The section was then moved vertically, again by the specific distance, and a second horizontal transverse was carried out. The number of fields counted on each horizontal transverse was dependent on the size of the section. Therefore, the distance between adjacent fields

Table 1 Demographic data of 41 cases of CGCG

Case no.	*Age/gender*	*Location*
1	2/M	Mandible, anterior
2	9/M	Mandible, body-ramus
3	13/M	Maxilla, molar
4	14/M	Maxilla, anterior
5	14/F	Mandible, premolar-molar
6	15/F	Mandible, premolar-molar
7	20/M	Mandible, molar
8	22/F	Mandible, premolar
9	22/F	Maxilla, molar
10	23/F	Maxilla, molar
11	24/F	Maxilla, anterior
12	25/F	Maxilla, anterior
13	25/F	Mandible, premolar
14	28/M	Mandible, right premolar-left lateral
15	28/F	Mandible, premolar
16	29/M	Mandible, premolar right-premolar left
17	29/F	Maxilla, canine-premolar
18	32/F	Mandible, premolar right-premolar left
19	33/F	Mandible, lateral-premolar
20	33/M	Maxilla, molar
21	37/M	Mandible, premolar-molar
22	37/M	Mandible, anterior
23	38/M	Maxilla, anterior
24	38/M	Maxilla, premolar
25	40/F	Maxilla, premolar-molar
26	41/F	Maxilla, canine-premolar
27	45/M	Mandible, premolar-ramus
28	45/F	Maxilla, anterior
29	46/F	Maxilla, canine
30	52/M	Mandible, anterior
31	53/F	Maxilla, molar
32	56/F	Mandible, premolar
33	56/M	Maxilla, anterior
34	57/M	Mandible, premolar
35	62/F	Mandible, molar
36	66/F	Maxilla, canine
37	68/M	Maxilla, premolar-tuberosity
38	70/F	Mandible, canine
39	72/F	Maxilla, lateral-canine
40	77/M	Mandible, canine
41	86/F	Mandible, anterior

CGCG, central giant cell granuloma; M, male; F, female.

was between one and four graticule widths. Results were expressed as percentage MVV per case after all 10 fields (i.e. total 1210 points) were examined from each section. The mean percentage MVV ± standard deviation was calculated for all 41 cases.

Quantification of bFGF-positive blood vessels within CGCG

The bFGF-stained slide of each lesion was submitted for stereologic assessment identical to that used for VEGF-stained slides. Results were presented as the percentage MVV per case and as mean percentage MVV ± standard deviation for all 41 examined cases.

Quantification of VEGF and bFGF-positive blood vessels at the periphery of CGCG tissue (control areas)

Measurements were taken at the periphery of the CGCG lesions, in the surrounding areas beneath the oral epithelium lining, in cases where the jawbone was perforated. As these areas were characterized by reactive inflammatory tissue, including numerous newly formed vascular structures, they served as controls (4). Control areas in five cases of CGCG were analyzed for the mean percentage MVV of VEGF- and bFGF-positive blood vessels in a manner identical to that previously described for the core of CGCG tissue.

Quantification of VEGF-positive MC and GC

The percentage of VEGF-positive MC and GC was estimated from the total number of the respective cell type in the entire section at ×100 magnification. As both MC and GC demonstrated a wide percentage range of positively stained cells, cases were classified in decreasing order of the percentage of the VEGF-positive MC. Staining in 50% or more of the cells was considered as high.

Quantification of bFGF-positive MC and GC

The percentage of bFGF-positive MC and GC was calculated as for VEGF. Staining in 50% or more of the cells was considered as high. Cases were presented in the same order used for VEGF staining, irrespective of the actual percentage of the bFGF-positive cells. In this manner, a parallel comparison of the percentage of VEGF- and bFGF-positive cells in each case was possible.

To maintain a consistent presentation of the study results, percentage of MVV of VEGF and bFGF stains per case appeared in the same case order as the percentage of VEGF and bFGF-positive cells. Quantifications were carried out by a single trained observer (MV).

Statistical analysis

Correlations between age and gender and VEGF and bFGF parameters were analyzed by using Spearman and Mann–Whitney tests, respectively. Correlations between the percentage MVV of VEGF- and bFGF-positive blood vessels within CGCG tissue were analyzed by using the Spearman test. Within CGCG lesions, differences in the mean percentage MVV between VEGF-positive and bFGF-positive blood vessels were analyzed by using the Wilcoxon signed ranks test. Differences in the mean percentage MVV of VEGF- and bFGF-positive blood vessels between CGCG tissue and control areas were analyzed by using the Wilcoxon signed ranks test. Statistical significance was at $P < 0.05$. The Statistical Package for the Social Sciences (SPSS 11) software was used for computations.

Results

General immunohistopathologic findings within CGCG

Hematoxylin- and eosin-stained slides showed numerous vascular spaces devoid of any endothelial lining usually filled with erythrocytes. Endothelial-lined blood vessels were not easily identified, but were visible following VEGF and bFGF staining procedures, which emphasized the lining endothelial cells. The VEGF- and bFGF-positive blood vessels dispersed throughout the lesional tissue were usually sparse, ranging in size from capillaries to medium-sized blood vessels. Frequently, the plump endothelial cells demonstrated incomplete circumferential staining as shown by both VEGF (Fig. 1) and bFGF stains (Fig. 2). Additionally, most lesions contained a considerable number of positively stained MC and GC. In general, the intensity of VEGF and bFGF staining was weaker in these cells compared with the positively stained endothelial cells. Nevertheless, a clear distinction could be made between positively stained and non-stained lesional cells (Fig. 1).

General findings in the surrounding tissue of CGCG – control areas

Hematoxylin- and eosin-stained slides showed control areas characterized by an abundance of blood vessels, usually of medium to large size and numerous inflammatory cells, mainly of chronic inflammation type, located adjacent and among the blood vessels. The immunohistochemically stained slides showed that these

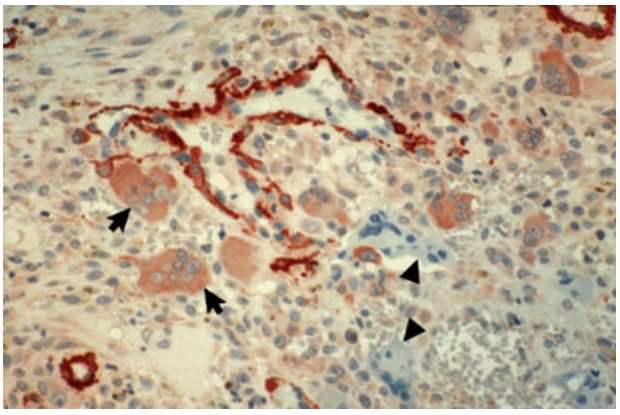

Figure 1 Photomicrograph of vascular endothelial growth factor (VEGF) immunostain within central giant cell granuloma tissue shows a medium size blood vessel with strongly reactive endothelial lining cells in the center. Positively stained giant cells (arrows) are seen adjacent to this central blood vessel. At the right lower corner, a vascular space devoid of endothelial lining is seen surrounded by giant cells without VEGF staining (arrow heads). Faint VEGF stain is also observed in the mononuclear cells (ABC method, ×200 original magnification).

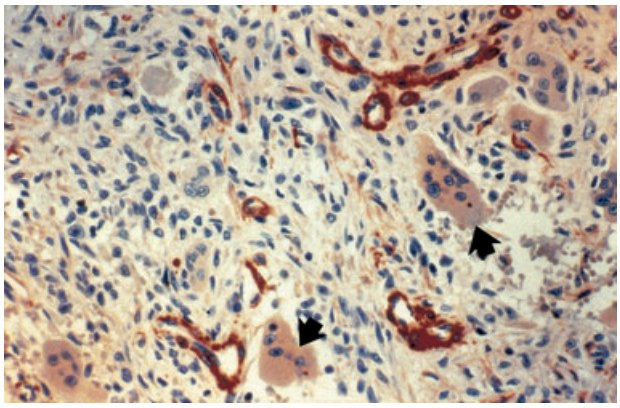

Figure 2 Photomicrograph of basic fibroblast growth factor (bFGF) immunostain within central giant cell granuloma tissue shows several small and medium-sized blood vessels with strongly reactive endothelial lining cells. A number of giant cells immunoreactive for bFGF (arrows) are seen adjacent to the positive blood vessels. Faint bFGF stain is also observed in the mononuclear cells (ABC method, ×200 original magnification).

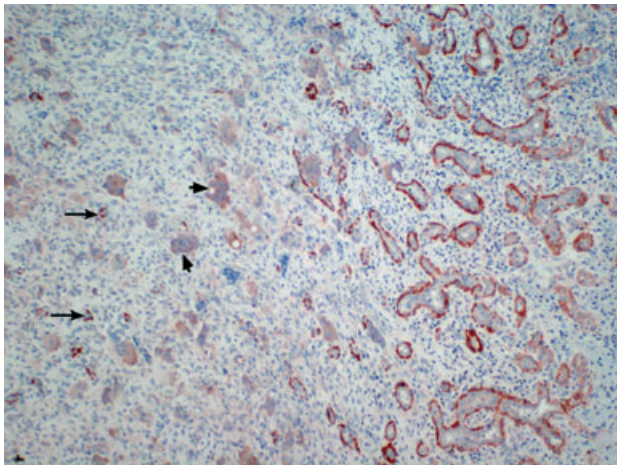

Figure 3 Abundance of vascular endothelial growth factor (VEGF)-positive blood vessels in reactive vascular-rich inflammatory areas in the surrounding of the central giant cell granuloma (CGCG) lesion (right upper corner). The CGCG lesion shows only a few small VEGF-positive blood vessels (arrows). Giant cells within CGCG tissue are usually VEGF positive (small arrows) (ABC method, ×100 original magnification).

blood vessels were strongly and diffusely positive for both VEGF (Fig. 3) and bFGF (Fig. 4).

Quantitative findings

Age and gender

No statistically significant correlations were found between age and gender and the examined VEGF and bFGF parameters ($P > 0.05$).

Percentage MVV of VEGF- and bFGF-positive blood vessels within CGCG

The MVV of VEGF was less than 5% in 36 (87.8%) lesions, between 5% and 10% in four (9.7%) lesions, and slightly higher than 10% in only one (2.5%) lesion (Fig. 5). The MVV pattern of bFGF-positive blood vessels was similar to that of VEGF, where MVV

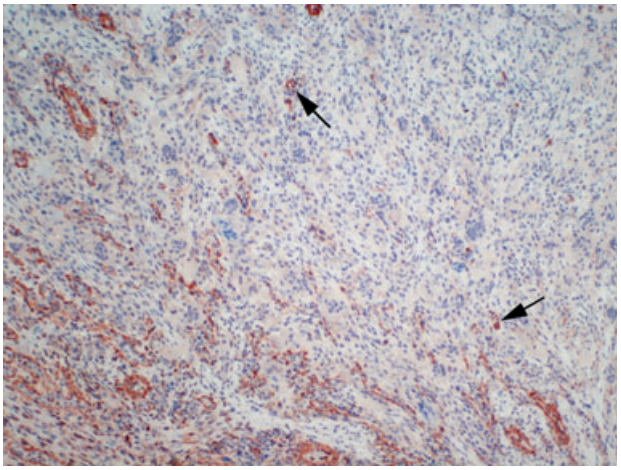

Figure 4 Abundance of basic fibroblast growth factor (bFGF)-positive blood vessels in reactive vascular-rich inflammatory areas in the surrounding of the central giant cell granuloma (CGCG) lesion (left lower corner). The CGCG lesional tissue shows only a few bFGF-positive dispersed small size blood vessels (arrows) (ABC method, ×100 original magnification).

of less than 5% was noted in 32 (78%) lesions, between 5% and 10% in eight (19.5%) lesions, and slightly higher than 10% in only one (2.5%) lesion. A strong positive correlation was found between the percentage MVV of VEGF- and that of bFGF-positive blood vessels ($R = 0.61$, $P < 0.001$, correlation significant at 0.01 level). The mean percentage MVV of bFGF-positive blood vessels was 3.5% ± 2.4% and statistically higher than that of VEGF-positive blood vessels (2.9% ± 2.4%, $P = 0.001$).

Mean percentage MVV of VEGF- and bFGF-positive blood vessels in the surrounding CGCG tissue – control areas

The mean MVV of VEGF- and bFGF-positive blood vessels was 27.5% ± 7.3% and 25.1% ± 5.5%, respectively, which was significantly higher than the mean percentage MVV of both VEGF- and bFGF-positive blood vessels within CGCG ($P = 0.043$).

Percentage of VEGF- and bFGF-positive MC and GC

In general, MC and/or GC positive for VEGF were found in 39 (95%) lesions (Fig. 6). Lesions were not homogeneously stained: high staining in both MC and GC (cases 1–20), high staining in either MC or GC (cases 21–35), and low staining (cases 36–41).

Mononuclear cells and/or GC positive for bFGF were found in 19 (46.3%) lesions (Fig. 7), which were markedly less compared with VEGF results. Lesions positive for VEGF in either cell type were not necessarily positive for bFGF in the same percentage and vice versa.

Discussion

The hypothesis that CGCG belongs to the spectrum of primary jaw proliferative vascular lesions has been proposed (5). However, characterization of the lesional vascular component has not been fully investigated.

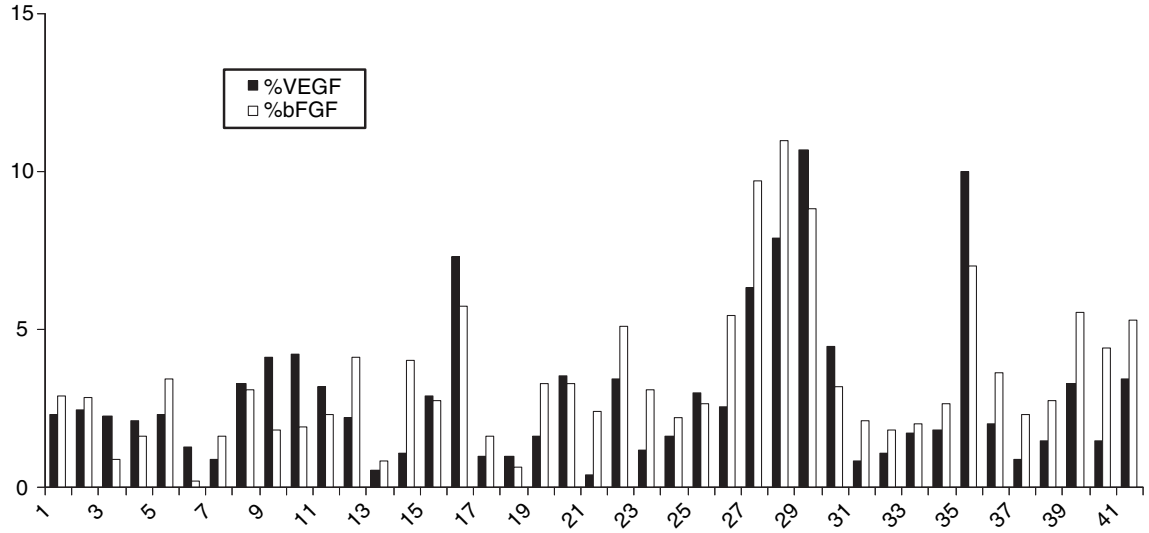

Figure 5 Microvascular volume of vascular endothelial growth factor (VEGF)- and basic fibroblast growth factor (bFGF)-positive blood vessel within central giant cell granuloma tissue.

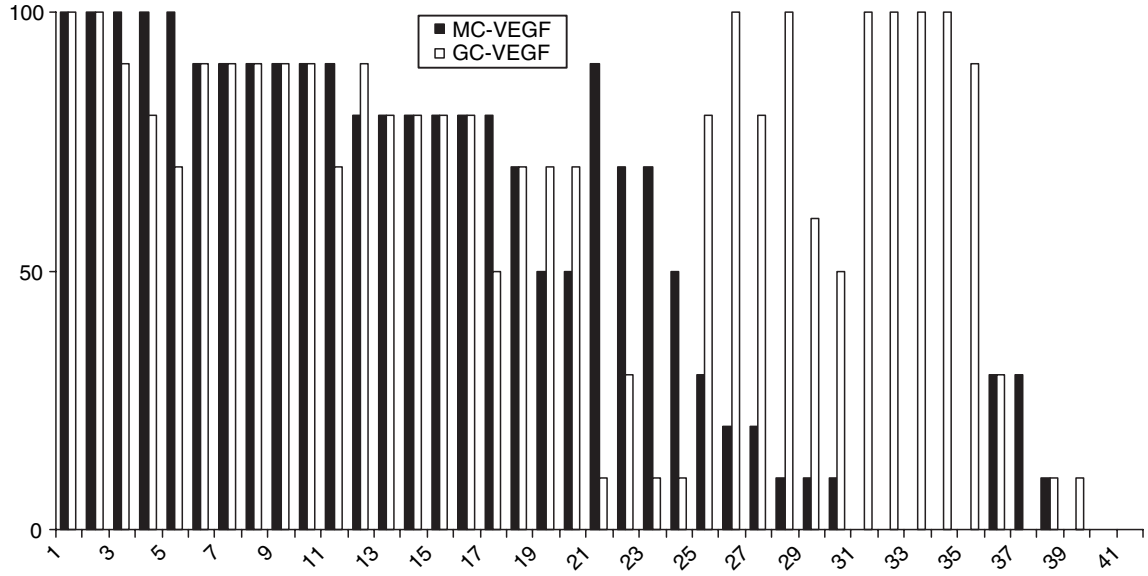

Figure 6 Percentage of vascular endothelial growth factor (VEGF)-positive mononuclear cells (MC) and giant cells (GC).

The present study showed that angiogenesis does occur within CGCG tissue. This was reflected by the immunoreactivity of endothelial cells of the lesional blood vessels to VEGF and bFGF, which would not be expected in endothelial cells of established vascularity (8, 10). Angiogenesis was limited, as indicated by the low mean MVV, less than 3% and 4% for VEGF- and bFGF-positive blood vessels, respectively. In contrast, the control vascular-rich inflammatory areas presented higher mean MVV for both VEGF (10-fold) and bFGF (sevenfold). These findings suggest that CGCG lesions cannot be defined as vascular proliferative lesions. This is in agreement with a previous study, which showed differences in vascularity between the core of CGCG tissue and their peripheral control regions that featured vascular-rich inflammatory zones (4). Markers, routinely used to detect established vascularity (e.g. factor VIII, Ulex europaeus 1 lectin and QBend 10), showed that blood vessels within CGCG were negatively stained, whereas inflammatory areas in the periphery of lesions yielded strong positive staining. This was interpreted as the absence of a mature functioning microvasculature within CGCG lesions (4).

Unlike the low frequency of VEGF and bFGF-positive blood vessels within CGCG lesions, the immunomorphometric results showed high immunoreactivity of the lesional cells to these angiogenic factors. Nearly

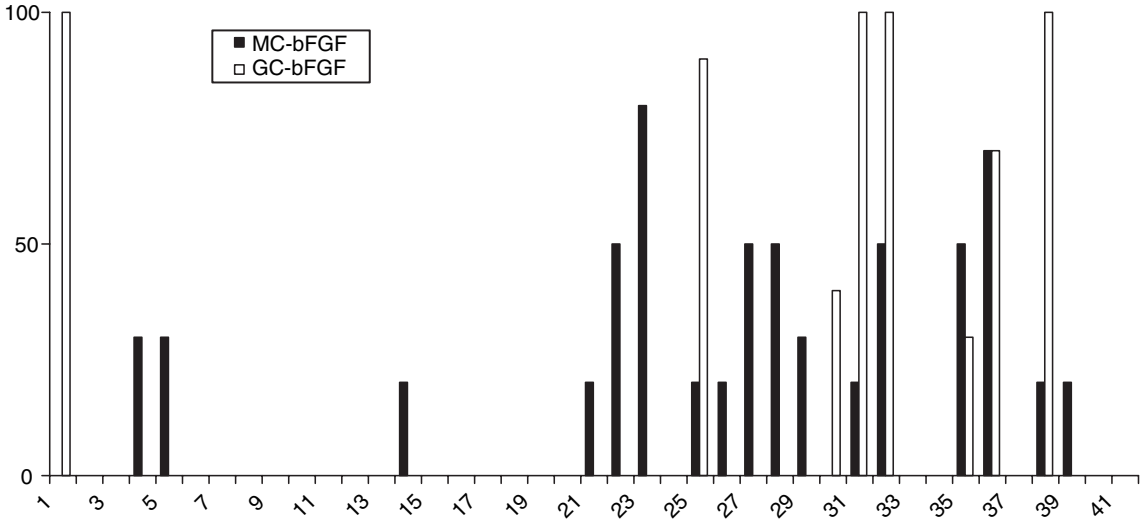

Figure 7 Percentage of basic fibroblast growth factor (bFGF)-positive mononuclear cells (MC) and giant cells (GC).

all lesions possessed MC and/or GC that demonstrated VEGF staining. Approximately half of the CGCG lesions also demonstrated bFGF staining in the MC and/or GC.

Studies of primary bone tumors, both benign and malignant, have demonstrated that many bone forming and bone resorbing cells, as well as vascular endothelial cells, are positive for VEGF, e.g. in osteoblastoma, both osteoblasts and osteoclast-like GC are unequivocally VEGF positive (18). Similarly, in osteogenic sarcoma, VEGF was detected in all examined lesions in both mononuclear and multinuclear tumor cells (18). Giant cell tumor of bones (GCTB), together with CGCG, could represent a continuing single disease process rather than being distinct and separate entities (19). In GCTB, VEGF was present in the mononuclear spindle- and round-shaped stromal cells, as well as in the osteoclast-like multinucleated GC (20, 21).

Central giant cell granuloma and other similar primary multinucleated giant cell-containing bone lesions share two main features: they are osteolytic lesions and harbor a considerable number of MC and GC positive for potent angiogenic factors. Therefore, a biologic link between these features must exist. The apparent 'provocative' issue of whether osteoclast function is dependent on endothelial cells and/or their associated factors has been raised (22). Increased local bone resorption and remodeling coincide with angiogenesis in normal bone development, fraction healing, and in pathologic conditions, such as inflammatory-related rheumatoid arthritis, periodontal diseases, tumor-associated osteolysis, and osteoporosis (15). This can be explained by the fact that stimulated angiogenesis facilitates increased delivery of immune and hematopoietic precursors to the lesion area. This results in a greater number of osteoclast precursors that can now emigrate from the peripheral circulation into the bone tissue and develop into bone-resorptive cells, a process termed osteoclastogenesis. Both VEGF and bFGF play a pivotal role in osteoclastogenesis, besides being potent angiogenic factors (15).

The present study showed that lesional cells (MC and GC) were a source for VEGF and bFGF, in addition to the endothelial cells. Furthermore, as CGCG has only a minor compartment of angiogenesis, the main burden of osteoclastogenesis is on the MC and GC rather than on the endothelial cells. It seems that MC and GC can promote the process of osteoclastogenesis in CGCG despite the absence of a prominent vascular component. Therefore, the more VEGF- and bFGF-producing cells in a CGCG lesion, the more aggressive biologic behavior is expected. In the present study, CGCG lesions were heterogeneous in their percentage of lesional cells positive for VEGF and bFGF. This can partially explain the differences in their behavior. In GCTB, it was suggested that overexpression of VEGF is associated with an advanced stage (20, 21). Given the assumption that CGCG is part of the GCTB spectrum, future studies should focus on the correlations between VEGF and bFGF-positive cells and biologic behavior of CGCG.

The fact that nearly 90% of CGCG were VEGF positive in a high percentage of the MC and/or GC, as shown in the present study, makes them an attractive target for anti-VEGF treatment. This includes dexamethasone, which at experimental and clinical levels has demonstrated that it can reduce the expression of VEGF (23). In CGCG, dexamethasone can be administered as intralesional injections. Furthermore, humanized anti-VEGF monoclonal antibodies have been developed and are currently in advanced clinical trials in different tumors, either alone or in combination with routine anti-neoplastic strategies (10, 14). The proposed therapeutic methods against VEGF and bFGF in CGCG should be clinically recommended only on a selective basis, particularly in cases in which the immunohistochemical stains confirm positivity for these markers.

References

1. Waldron CA. Bone pathology. In: Neville BW, Damm DD, Allen CA, Bouquot JE, eds. *Oral and maxillofacial pathology*. Philadelphia, PA: Saunders, 1995; 453–5.
2. Li B, Yu S-F, Li T-J. Multinucleated giant cells in various forms of giant cell containing lesions of the jaws express features of osteoclasts. *J Oral Pathol Med* 2003; **32**: 367–75.
3. Itonaga I, Hussein I, Kudo O et al. Cellular mechanism of osteoclast formation and lacunar resorption in giant cell granuloma of the jaws. *J Oral Pathol Med* 2003; **32**: 224–31.
4. Lim L, Gibbins JR. Immunohistochemical and ultrastructural evidence of a modified microvasculature in the giant cell granuloma of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; **79**: 190–8.
5. Kaban LB, Troulis MJ, Ebb M et al. Antiangiogenic therapy with interferon alpha for giant cell lesions of the jaws. *J Oral Maxillofac Surg* 2002; **60**: 1103–11.
6. Kaban LB, Mulliken JB, Ezekowitz RA et al. Antiangiogenetic therapy of a recurrent giant cell tumor of the mandible with interferon alpha-2a. *Pediatrics* 1999; **103** (6 Pt 1): 1145–9.
7. Collins A. Experience with anti-angiogenic therapy of giant cell granuloma of the facial bones. *Ann R Australas Coll Dent Surg* 2000; **15**: 170–5.
8. Seghezzi G, Patel S, Ren CJ et al. Fibroblast growth factor–2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: an autocrine mechanism contributing to angiogenesis. *J Cell Biol* 1998; **141**: 1659–73.
9. Leung DW, Cachianes G, Kuang W-J et al. Vascular endothelial factor is a secreted angiogenic mitogen. *Science* 1989; **246**: 1306–12.
10. Ferrara N, Gerber H-P, Le Couter J. The biology of VEGF and its receptors. *Nat Med* 2003; **9**: 669–76.
11. Bocci G, Fasciani A, Danesi R et al. In vitro evidence of autocrine secretion of vascular endothelial growth factor by endothelial cells from human placental blood vessels. *Mol Hum Reprod* 2001; **7**: 771–7.
12. Tolany E, Kuhnen C, Voss B et al. Expression and localization of vascular endothelial factor and its receptor flt in pulmonary sarcoidosis. *Virchows Arch* 1998; **432**: 61–5.
13. Pakala R, Watanabe T, Benedict CR. Induction of endothelial proliferation by angiogenic factors released by activated monocytes. *Cardiovasc Radiat Med* 2002; **3**: 95–101.
14. Ferrara N. VEGF and the quest for tumour angiogenesis factors. *Nat Rev Cancer* 2002; **2**: 795–803.
15. Collin-Osbody P, Rothe L, Bekker S et al. Basic fibroblast growth factor stimulates osteoclast recruitment, development, and bone pit resorption in association with angiogenesis *in vivo* on the chick chorioallantoic membrane and activates isolated avian osteoclast resorption *in vitro*. *J Bone Miner Res* 2002; **17**: 1859–71.
16. Carlile J, Harada K, Baillie R et al. Vascular endothelial growth factor (VEGF) expression in oral tissues: possible relevance to angiogenesis, tumor progression and field cancerization. *J Oral Pathol Med* 2001; **30**: 449–57.
17. Macluskey M, Chandrachud LM, Pazouki S et al. Apoptosis, proliferation, and angiogenesis in oral tissues. Possible relevance to tumor progression. *J Pathol* 2000; **191**: 268–75.
18. Sulzbacher I, Birner P, Trieb K et al. Expression of osteopontin and vascular endothelial growth factor in benign and malignant bone tumors. *Virchows Arch* 2002; **441**: 345–9.
19. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. *Oral Surg Oral Med Oral Pathol* 1993; **75**: 199–208.
20. Zheng MH, Xu J, Robbins P et al. Gene expression of vascular endothelial growth factor in giant cell tumors of bone. *Hum Pathol* 2000; **31**: 804–12.
21. Kumta SM, Huang L, Cheng YY et al. Expression of VEGF and MMP-9 in giant cell tumor of bone and other osteolytic lesions. *Life Sci* 2003; **73**: 1427–36.
22. Folkman J. Antiangiogenetic therapy with interferon alpha for giant cell lesions of the jaws (comment). *J Oral Maxillofac Surg* 2002; **60**: 1111–3.
23. Heiss JD, Papavassiliou E, Merrill MJ et al. Mechanism of dexamethasone suppression of brain tumor-associated vascular permeability. *J Clin Invest* 1996; **98**: 1400–8.

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