Original Article

An insight into the cannibalistic behavior of giant cell granulomas of the jaws

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Abstract

Background: Cellular cannibalism is defined as a large cell engulfing a smaller one within its cytoplasm. It is predominantly a feature of aggressive malignancies but has recently been demonstrated in giant cell (GC) lesions such as GC tumor of tendon sheath, central GC granuloma (CGCG) and peripheral GC granuloma (PGCG).

Aim: The aim of the study is to assess the cannibalistic GCs in CGCG and PGCG and correlate with aggressiveness of the lesion.

Settings and Design: Archival data of histopathologically confirmed cases of CGCG ($n = 40$) and PGCG ($n = 25$) were studied in the Department of Oral Pathology, Maulana Azad Institute of Dental Sciences.

Materials and Methods: Quantification of cannibalistic cells was performed using H&E stain on microscopic sections. One hundred GCs were examined in each slide, and the number of cannibalistic cells was expressed in percentage.

Results: GC cannibalism was observed in all cases. The mean number of cannibalistic GCs in CGCG was 44.67 which was significantly higher ($P = 0.028$) than PGCG (mean 28.04). In aggressive ($n = 18$) CGCG, the mean number of cannibalistic GCs was 51.27 which was significantly higher ($P = 0.019$) than cannibalistic GCs in nonaggressive ($n = 22$) CGCG (mean 39.27). No significant difference was observed between the number of cannibalistic cells in recurrent (mean = 52.9) and nonrecurrent (mean = 49.2) cases of CGCG ($P > 0.05$). Two of the nine cases treated initially by steroid showed fewer and smaller cannibalistic GCs with vesicular nuclei.

Conclusion: There was a clear distinction in the mean cannibalistic count between aggressive and nonaggressive CGCG. Hence, the aggressiveness of the lesion could be assessed following which appropriate treatment modality can be constituted.

Keywords: Cannibalism, central giant cell granuloma, giant cells, peripheral giant cell granuloma

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INTRODUCTION

Cannibalism is the term used to describe "cell-eat-cell" phenomenon. The word cannibalism is derived from "Cannibals," a Spanish name for the Carib people known for eating flesh or internal organs of other human beings.[1-3] Cellular cannibalism is defined as "a large cell enclosing a slightly smaller one within its cytoplasm." It was first described by Leyden, in 1904, who named these cells as "bird's eye cells" or "signet ring cells" because of its appearance. The engulfed cell during this process

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is still alive, but the process implies its death.[1,4,5] After engulfment, the cells undergo cell death or divide inside the vacuoles or sometimes escape to re-emerge as a cell that is indistinguishable from their unengulfed counterparts.[1]

Cellular cannibalism is a characteristic morphologic feature exclusively seen in aggressive malignancies and has been described in breast carcinoma, giant cell (GC) carcinoma of the lung, gallbladder carcinoma, endometrial stromal carcinoma, malignant thymoma, malignant melanoma and oral squamous cell carcinoma (OSCC).[5-10] Demonstration of cannibalistic cells in these malignant lesions has been correlated well with the aggressiveness, degree of anaplasia, invasiveness and metastatic potential. However, the role of cellular cannibalism is not fully understood: It may function as a way of eliminating malignant cells or the ingested cell may serve as a source of nutrition for the proliferating cell that shows this cannibalistic behavior.[2]

Recently, cellular cannibalism has also been demonstrated in GC lesions such as GC tumor of tendon sheath of localized type, central GC granuloma (CGCG) and peripheral GC granuloma (PGCG) of the oral cavity.[3,4] An increased number of cannibalistic GCs in PGCG and CGCG represents high metabolic activity in the GCs and can be correlated with the aggressive biological behavior of the lesions.[4] The aim of the study was to identify and quantify the cannibalistic GCs on routine H&E-stained sections of CGCG and PGCG of the jaws and evaluate its clinicopathological features with the aggressiveness of the lesion and thus aid in better treatment planning.

MATERIALS AND METHODS

Case selection

Cases of CGCG and PGCG were reviewed from the archival data of the Department of Oral Pathology and Microbiology, Maulana Azad Institute of Dental Sciences, New Delhi, from January 2011 to December 2015. Forty cases of CGCG and 25 cases of PGCG with adequate clinical and radiographic documentation were finally selected. According to the research guidelines of our institute, retrospective studies do not require ethical approval. However, informed consent was taken from those patients whose clinical and radiographic photographs were used for publication purpose.

Classification of cases of central giant cell granuloma

The lesions of CGCG were classified as nonaggressive or aggressive based on the criteria established by Chuong *et al*. and validated by several other studies on the biological behavior of CGCG.[4,11-13] Cases with a history of pain, rapid growth, root resorption and cortical perforation with a tendency to recur were classified as aggressive CGCGs [Figure 1a]. Cases with a history of minimal or no symptoms, slow growth, absence of root resorption or cortical perforation and no tendency to recur were classified as nonaggressive CGCG [Figure 1b]. All cases had been treated by modalities ranging from curettage to intralesional corticosteroid injections and surgery. Follow-up data were available for all cases till 2 years.

Cases of peripheral giant cell granuloma

Further categorization of cases of PGCG was not done as it is a peripheral soft tissue lesion with no aggressive potential.

Quantification of cannibalistic cells

H&E-stained slide of each case was reviewed by two independent histopathologists. One hundred GCs were examined in each slide, and the number of cannibalistic cells was expressed in percentage. All sections were examined under higher magnification (×400). Battle field (zig-zag) method was used for counting the GCs to avoid recounting of the same cell.

Identification of cannibalistic cells

CGCG and PGCG show a predominance of foreign body type of GCs. Hence, multinucleated cells with randomly arranged nuclei were identified as foreign body GCs and were then scanned for cannibalistic features based on the morphologic alterations evident under light microscopy. The identification of cannibalistic GCs was performed on routine H&E-stained sections. Cannibalistic GCs showed either partial or complete cannibalism of mononuclear stromal cells. Partial cannibalism showed pseudopod formation by cannibalistic GCs around the mononuclear

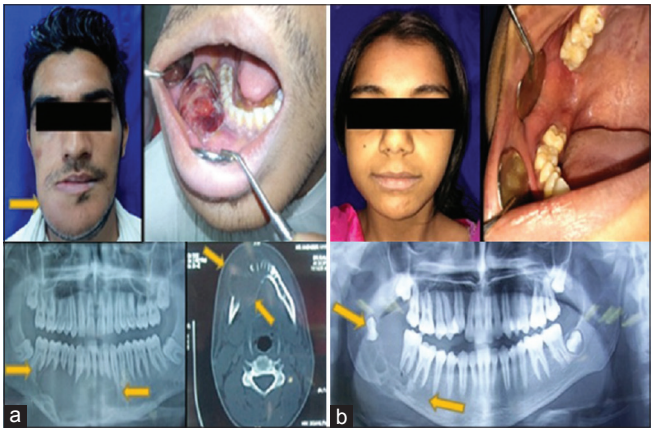

Figure 1: (a) Aggressive central giant cell granuloma in 18-year-old male patient extending from 33 to 48 showing the clinical and radiographic presentation, (b) nonaggressive central giant cell granuloma in 17-year-old female patient extending from 46 to 48 showing the clinical and radiographic presentation

stromal cells. At the interface of the mononuclear cell and the cell membrane of GC, a small concavity on the cell membrane of GC could be seen. In complete cannibalism, the mononuclear cell was present completely enclosed within the cytoplasm of cannibalistic GC. In such instances, the internalized mononuclear cell was surrounded by a clear halo.[12,13] As GCs originate from the fusion of mononuclear cells, cannibalism can be confused with the formation of GC by the fusion of mononuclear cells. However, striking features such as a clear halo around the internalized cell (mononuclear cell) and concavities on the plasma membrane of GC are the most vital features to identify cannibalism.

Statistical analysis

The mean number of cannibalistic GCs was calculated for each group, and the differences were analyzed by the unpaired Student's *t*-test. $P < 0.05$ was considered statistically significant. Computations were carried out using the SPSS software version 22.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Demographic results

The mean age of patients with CGCG was 21.57 years and with PGCG was 28.04 years. Female predilection with a ratio of 2.3:1 was observed among patients with CGCG, whereas there were almost equal numbers of female and male patients in PGCG. The most common site for both CGCG and PGCG was posterior mandible. Among patients with CGCG, 18 cases were clinically classified as aggressive CGCG and 22 cases were classified as nonaggressive. Follow-up data till 2 years were available for all cases with recurrence seen in six cases of CGCG.

Histopathological features of giant cells

GC cannibalism was observed in all the cases (100%) of CGCG and PGCG. The cannibalistic GCs showed either partial or complete cannibalism or both types of cannibalism of the stromal cells. In partial cannibalism, pseudopod formation by cannibalistic GCs was observed [Figure 2a]. The completely cannibalized cells were seen in the cytoplasm surrounded by a clear halo [Figure 2b]. Many GCs engulfing more than one cell were also observed [Figure 3a]. In the final stage, completely internalized cells undergone apoptosis appear as an empty vacuole [Figure 3b]. Minor differences were observed in the cannibalistic features of CGCG when treated by initial phase of steroids over surgical curettage.

Comparison of giant cells in central giant cell granuloma and peripheral giant cell granuloma

The mean number of cannibalistic GCs was 44.67 ± 5.45 in CGCG and 29.20 ± 4.87 in PGCG. The cannibalistic GCs were significantly higher ($P = 0.028$) in CGCG as compared to PGCG. In aggressive CGCG, mean cannibalistic GCs was 51.27 which was also significantly higher ($P = 0.019$) than the mean cannibalistic GCs in nonaggressive CGCG (mean 39.27) [Table 1]. The mean

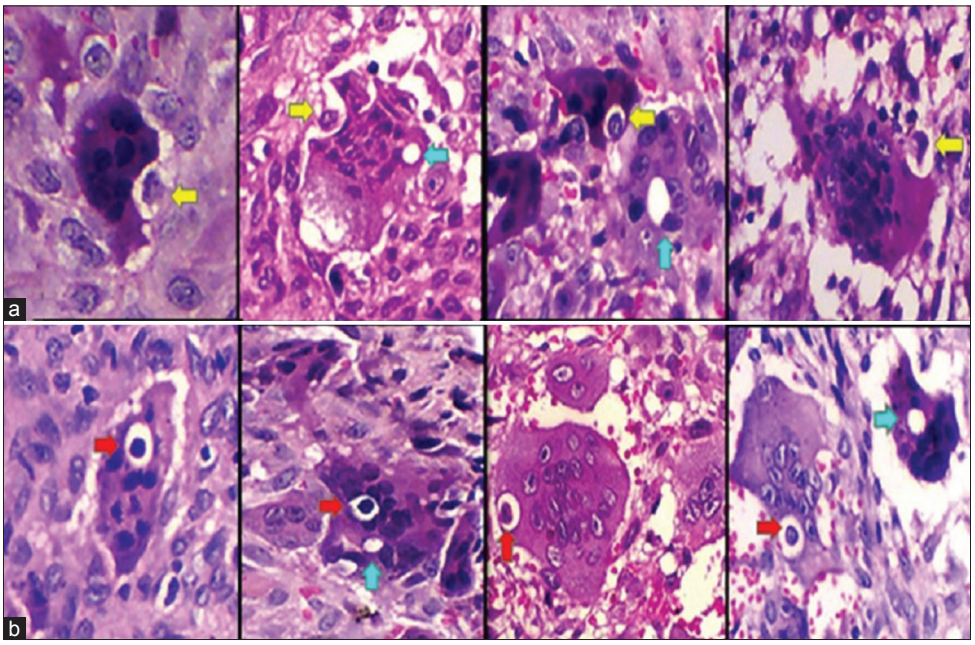

Figure 2: (a) Partial cannibalism-cannibalistic giant cells initiating to engulf the stromal cells by pseudopod formation (yellow arrow) (H&E, ×400), (b) complete cannibalism - stromal cells completely internalized within the cytoplasm of giant cells (red arrow). Stromal cells undergoing apoptosis within the cannibalistic giant cells are also shown (blue arrow) (H&E, ×400)

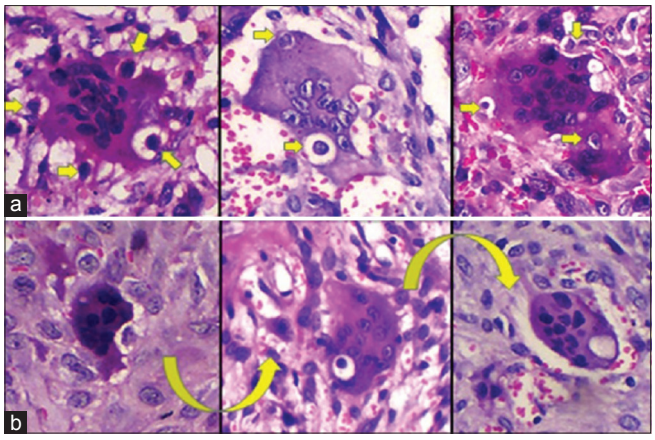

Figure 3: (a) Complex cannibalism – single giant cell engulfing more than one stromal cell (H&E, ×400), (b) various stages of cannibalism. Initial stage of attachment of stromal cell to the surface of giant cell and partial engulfment by pseudopod formation. Subsequent internalization of stromal cell within the cytoplasm of the giant cell. Final stage of apoptosis and cell death of the internalized stromal cell (H&E, ×400)

number of cannibalistic cells in recurrent cases of CGCG was higher (mean = 52.9) than the mean cannibalistic cells of nonrecurrent cases of CGCG (mean = 49.2) although the difference was not statically significantly ($P > 0.05$). Two of the nine cases treated initially by steroid showed fewer and smaller cannibalistic GCs with vesicular nuclei.

DISCUSSION

Cellular cannibalism is not a new phenomenon in pathology; however, its significance and presence are still not fully understood. Cannibalism has been described as an exclusive property of malignant tumor cells. It has been associated with the degree of anaplasia, invasiveness, aggressiveness and metastatic potential of various malignancies such as breast cancer, malignant melanoma, GC carcinoma of lung, gallbladder carcinoma, endometrial stromal carcinoma and malignant thymoma.[9,14,15]

Cellular cannibalism is fundamentally different from other forms of cell eating, such as phagocytosis, entosis, emperipolesis and autophagy, but can imitate these phenomena.[15] Cannibalism is the active internalization and destruction of either dead or living tumor cells by other engulfing cells; emperipolesis is the engulfment of intact hematopoietic cells, mainly neutrophils, lymphocytes and plasma cells by host cancer cells wherein the internalized cells are not destroyed; and entosis is a mechanism of homogenous live-cell invasion resembling a parasite–cell interaction, such that the invading cell seems to take the initiative in being internalized.[16-21]

The present study investigated the role of cannibalism in GC formation as well as in progression and aggressiveness

Table 1: Mean cannibalistic giant cells in peripheral giant cell granuloma and central giant cell granuloma

Groups (*n*=number of cases)	Mean number of cannibalistic giant cells±SD	*P*
CGCG (*n*=40)	44.67±5.45	0.028
PGCG (*n*=25)	29.20±4.87	
Aggressive CGCG (*n*=18)	51.27±6.56	0.019
Nonaggressive CGCG (*n*=22)	39.27±4.89	
Recurrent CGCG (*n*=6)	52.9±3.25	>0.05
Nonrecurrent CGCG (*n*=34)	49.2±4.18	

SD: Standard deviation, CGCG: Central giant cell granuloma, PGCG: Peripheral giant cell granuloma

of GC-containing lesions. GCs arise from the fusion of nonreplicating monocytes or from the mitotic and amitotic division of monocyte nuclei in the absence of cellular division (failed cytokinesis).[22] Thus, cannibalism, a form of cell internalization, might arguably be related to the formation of GCs from mononuclear cells.[23] Athanasou *et al*. also described in their ultrastructural study how GCs were admixed with mononuclear cells.[24] Cannibalism also leads to polyploidy as internalized cells disrupt cytokinesis of their engulfing cell hosts. By this mechanism, cannibalistic cell behavior can promote tumor progression by inducing aneuploidy.[25] Thus, cannibalism by GCs can contribute either to their formation or proliferation.

CGCG is a benign intraosseous lesion. The true nature of CGCG is unknown, and it is not ascertained as either a reactive, hamartomatous or neoplastic process. It can be that there is a reactive form (nonaggressive CGCG) and a neoplastic form (aggressive CGCG) and scientists have not been able to devise tools to scientifically separate the two. An aggressive model of CGCG has been proposed on the basis of clinical and radiological findings which characterize aggressive GC lesions on the presence of pain, paresthesia, a size of more than 5 cm, rapid growth, tooth displacement or root resorption and cortical bone thinning or perforation.[11,12]

PGCG is a frequent GC lesion of the jaws and originates from the connective tissue of the periosteum or the periodontal membrane. It is not a true neoplasm but rather a benign hyperplastic reactive lesion. The GCs of these pathologies are derived from monocyte-macrophage lineage and resemble osteoclasts. Hence, GCs in PGCG and CGCG possess inherent property of engulfment which is responsible for cannibalism of stromal tumor cells.[26]

The mean age of patients of CGCG in the present study was 21.57 years, whereas in PCGC, the mean age of occurrence was found to be 28.04 years which was in accordance with previous studies.[11,27,28] As reported in literature, a strong female predilection was seen in CGCG.[11-13,27] PGCG showed equal number of cases in males and females which was in contrast to few of the

earlier studies which reveal a female predilection.[28] Most of the cases of CGCG as well as PGCG presented in the posterior mandible although anterior mandible has been reported as the most common site in CGCG.[11-13,27]

In the current study, GC cannibalism was observed in all the cases (100%) of CGCG and PGCG. Fernandez-Flores studied 66 cases of GC tumor of the tendon sheath (localized type) and found GC cannibalism in 56 cases (84.34%).[3] Sarode and Sarode have demonstrated GC cannibalism in all cases of CGCG and PGCG (100%).[4] This finding suggests that GC cannibalism is more frequently seen in CGCG and PGCG as compared to GC tumor of the tendon sheath (localized type).

The present study demonstrates different stages found in cellular cannibalism [Figure 3b] as proposed by Brouwer *et al*.[26] The initial process starts with the attachment of cannibalistic cell to a free cell. Various dynamics hold cells together at cell–cell junctions. Any imbalance in adhesion forces between two cells may result in engulfment, with one cell pulling the other cell more strongly wherein the cell that has been pulled strongly is engulfed. It is followed by gradual engulfment of the cell cytoplasm of the free cell, with alteration of the nucleus of the cannibalistic cell to semilunar shape; however, the nucleus of the free cell remains unaltered. Eventually, the free cell gets completely interiorized within the cannibalistic cell and finally dies.

Until recently, cannibalism was recognized as a phenomenon mostly related to tumors against tumors cells. However, some reports suggested that tumor cell cannibalism may involve engulfment of other cells, such as neutrophils, lymphocytes and erythrocytes, in turn implying that cannibal tumor cells do not distinguish or select between the normal and sibling neoplastic cells. Thus, cannibalistic cells have no selectivity. It can affect the dead or living cells and involve either homogenous (cells of same type) or heterogeneous (cells of different type) cells.[9,13]

In the current study, an interesting observation was that the type of cannibalism found was of heterogenous type. The cannibalistic GCs showed either partial [Figure 2a] or complete [Figure 2b] or both type of cannibalism of the stromal cells. Complex cannibalism, i.e., GCs engulfing more than one cell, was also observed [Figure 3a]. In the present study, this feature of complex cannibalism was observed more frequently in CGCG than PGCG although the difference was statistically nonsignificant.

The mean number of cannibalistic GCs in CGCG and PGCG was 44.67 and 29.20, respectively. The cannibalistic CGs were significantly higher in CGCG as compared to PGCG with $P = 0.028$. Among patients with CGCG, 18 cases were clinically classified as aggressive CGCG and 22 cases were classified as nonaggressive according to criteria established by Chuong *et al*.[11] In aggressive CGCG, the mean number of cannibalistic GCs was 51.27 which was also significantly higher ($P = 0.019$) than the mean number of cannibalistic GCs in nonaggressive CGCG (mean = 39.27). The mean number of cannibalistic cells in recurrent cases of CGCG was higher (mean = 52.9) than the mean number of cannibalistic cells of nonrecurrent cases of CGCG (mean = 49.2) although the difference was not statically significantly ($P > 0.05$). Two of the nine cases treated initially by steroid showed fewer and smaller cannibalistic GCs with vesicular nuclei.

The results were in accordance with the recent study of Sarode and Sarode, who demonstrated that CGCG had higher cannibalistic GC frequency (38.06 ± 10.15) than PGCG (30.04 ± 5.63). In aggressive CGCG, mean cannibalistic GC frequency was significantly higher (42.20 ± 10.4) than nonaggressive variant (31.17 ± 6.014).[4] Thus, the increased frequency of cannibalistic GCs in CGCG in comparison to PGCG points toward the more aggressive behavior of CGCG. Furthermore, the increased value of cannibalistic GCs in aggressive CGCG in comparison to nonaggressive CGCG substantiates its increased aggressive potential.

Correlation of cannibalism with aggressiveness of the lesion, as observed in the present study, is substantiated by few studies in the past. According to a recent study by Sarode *et al*. in 2016, GCT which is a more aggressive lesion than CGCG, as explained by the higher expression of Ki-67 and p63, showed significantly higher mean cannibalistic GC frequency (44.81 ± 1.013) than CGCG (32.06 ± 1.398).[29] In another study, 100 cases of malignant effusion were analyzed by Bansal *et al*. The cannibalistic cells were more common in effusions with disseminated malignancy compared with cases of contiguous, local spread.[30] Sarode *et al*. noticed the presence of cannibalistic cells in OSCC and suggested that increase in number of cannibalistic cells was significantly associated with lymph node metastasis. Hence, cannibalism was considered one of the important parameters to note the aggressive nature of OSCC.[10]

Although cellular cannibalism is a thoroughly researched phenomenon in malignant tumors, there is a paucity of literature regarding cannibalism in benign lesions. The presence of cannibalistic activity in monocyte-macrophage-derived GCs can be considered as a prognostic feature to predict the clinicopathological aggressiveness and the recurrence rate of the lesion. The

study histopathologically illustrates different stages of cannibalism. It also throws light on different types of cannibalism such as simple or complex, partial or complete, homo or xeno cannibalism. Significantly, higher number of GC in clinically aggressive cases of CGCG indicates the use of cannibalism to predict the biological behavior of GC lesions and thus aid in better treatment planning. This was in concordance with past studies, but the current study had a much larger sample size than previous studies. Another interesting finding was that few cases treated initially by steroid showed fewer and smaller cannibalistic GCs with vesicular nuclei. Furthermore, recurrent cases showed higher number of mean cannibalistic cells than non recurrent cases, though the difference was statistically insignificant.

CONCLUSION

Thus, studying cannibalism in GC lesions could help in better understanding of the difference in varied clinical presentation ranging from a quiescent lesion with absence of symptoms to an aggressive pathological process, characterized by pain and rapid growth, and also aid in better treatment planning. Cellular cannibalism has easily identifiable morphological features under light microscopy without the use of any advanced and expensive molecular techniques. In future, extensive studies employing special investigations, such as immunohistochemistry with apoptotic markers and more sophisticated microscopic techniques such as phase-contrast microscopy or confocal microscopy, are required in other GC lesions to further study the role of cannibalism in the formation and function of GCs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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