Giant Cell Granuloma of the Temporal Bone
A Case Report With Immunohistochemical, Enzyme Histochemical, and In Vitro Studies

Xue-Fei Tian, MDS; Tie-Jun Li, PhD; Shi-Feng Yu, MD

REPORT OF A CASE
On July 10, 2000, a 32-year-old man was admitted to our hospital for a painless swelling in the right preauricular area during the past year. He had a history of otitis media but denied any previous experience of trauma. Physical examination revealed a 2.5 × 4.0-cm mass with slight tenderness to palpation in the right preauricular area expanding toward the right temporomandibular joint (TMJ) region. There was no alteration in the appearance of the skin and there were no palpable nodes in the neck. Facial nerve weakness and jaw motion limitation were not detected. Fine-needle aspiration biopsy was performed and the features were suggestive of a central giant cell lesion. Endocrinologists were consulted and hyperparathyroidism was excluded because serum alkaline phosphatase, serum inorganic phosphate, and calcium were all within the normal limits. On July 14, an incisional biopsy was carried out and diagnosis of GCG was confirmed. On July 30, the lesion was exposed through a preauricular incision and visualized as a brittle, brown-purple, granulation tissue mass with no capsule. Thoracic curetage of the lesion was carried out with special care to avoid damage of the dura mater. Postoperative healing was uneventful. At 26 months follow-up, there was no sign of recurrence.

MATERIALS AND METHODS
Paraffin-embedded sections of formalin-fixed tissue were studied by routine histology using hematoxylin-eosin stain. Immunostainings for CD68, myeloid/histiocyte antigen (MAC387), α-1-antitrypsin (AAAT), α-1-antichymotrypsine (AACT), lysozyme, and Ki-67 were performed using a sensitive biotin-streptavidin immunoperoxidase technique on 4-μm paraffin sections (Table). Tartrate-resistant acid phosphatase (TRAP) staining was performed on the cryostat sections using a leukocyte acid phosphatase kit (Sigma, St Louis, Mo).

Fresh specimens of the lesion were used for tissue culture studies. The tissue segments were finely minced with sterile scissors in alpha-minimum essential medium (α-MEM; HyClone, Logan, Utah) containing 15% fetal bovine serum, 25 mM Hepes, and antibiotics (100 U/mL penicillin and 100 μg/mL streptomycin). One milliliter of the resulting cell suspension was added to each well of a 12-well culture plate containing either sterilized glass coverslips or antiseptic bovine cortical bone ground slices (15 mm). After incubation at 37°C for 1 h to allow multinuclear giant cells to settle onto the coverslips or bone slices, less adhesive cells were washed away by pipetting with the culture medium. Each coverslip or bone slice was then moved to fresh α-MEM and incubated at 37°C in humidified air with 5% CO₂ for up to 4
days. After being cultured for 24 hours, the coverslips were fixed in 37% formaldehyde and stained for TRAP. Bone slices cocultured with the cell suspension were observed daily under a reverse-phase contrast microscope.

**PATHOLOGIC FINDINGS**

Histologically, the lesion was made up of a fibrillar connective tissue stroma with oval and spindle-shaped mononuclear cells and small capillaries. Numerous multinuclear giant cells were dispersed in the connective tissue background (Figure 2, A). These giant cells varied in shape and size and tended to cluster in uneven foci. The number of nuclei within the giant cells diversified from 5 to 40. Foci of hemorrhage were obvious. Hemosiderin deposition in mononuclear cells was prominent and a certain number of MGCs contained iron pigments or erythrocytes. Areas of newly formed bone or osteoid structure rimmed by osteoblasts were present. In general, pleomorphism and mitoses were unremarkable in the lesion.

**Figure 1.** Computed tomographic scan demonstrating a soft-tissue mass (circle number 1, arrow) in the anterior portion of the right temporal bone causing marked bone destruction (circle number 2, arrow).

Histochemical staining for TRAP on the cryostat sections revealed that virtually all the MGCs contained red-purple intracytoplasmic granules and some mononuclear cells in the lesion also showed a similar histochemical reaction (Figure 2, B). The results of the immunohistochemical evaluation are summarized in the Table. Almost all the MGCs within the lesion showed strong immunoreactivity for CD68, with only some of the mononuclear cells exhibiting a moderate reactivity (Figure 2, C). Other histiocyte/macrophage markers like MAC387, AAT, AACT, and lysozyme were also detected in the MGCs as well as in the mononuclear cells, but in a more patchy manner. Ki-67-positive nuclei were seen almost exclusively in the mononuclear cells, but the MGCs showed no reactivity (Figure 2, D).

Adherent cells in primary culture appeared 1 hour after dispersion from the lesion tissue. Cells included large multinuclear giant cells and a heterogeneous population of mononuclear cells, some of which were fibroblastlike and others rounded cells with morphologic features of lymphocytes or monocyte-macrophages (Figure 3, A). The adherent MGCs on the coverslips showed a strong reactivity for TRAP. When cocultured with the pretreated bovine cortical bone ground slices, the TRAP+ MGCs exhibited the ability to excavate resorption lacuna on the bone slices after 1 day of culture, and the number and the size of the resorption pits increased with time (Figure 3, B).

**COMMENT**

The first account of GCG in the temporal bone was recorded by Hirschl and Katz in 1974. Before their description, almost all giant cell lesions of the temporal bone were regarded as giant cell tumors (GCT). From a clinicopathologic point of view, the importance of distinguishing GCG from GCT lies in the presumed difference in prognosis, with GCT reportedly having a higher incidence of recurrence, metastasis, and malignant transformation. GCG occurs predominantly in the jaws and GCT in the epiphyses of the long bones. However, both of these lesions are rare in the skull. On histologic evaluation, a general consensus exists regarding the features of classic GCG and GCT. GCG is composed of small, elongated or oval-shaped stroma cells admixed with multinuclear giant cells. GCT also contains the two similar types of cells, but the giant cells are larger in size and more numerous. Giant cells in GCG tend to have fewer nuclei and irregular shapes and to cluster in uneven patches or foci, while those in GCT are more evenly distributed with a more uniform appearance. There is an increased incidence of osteoid, hemorrhage, and hemosiderin in GCG compared with GCT. Other mentioned characteristics include increased fibrosis and the absence of necrosis in GCG, and a greater incidence of mitotic figures in GCT. However, considerable overlap of characteristics between the two lesions exists. Attempts to correlate the histologic characteristics to the clinical behavior of these lesions appear to yield ambiguous results and no consensus currently exists on the histologic criteria that distinguishes aggressive from nonaggressive lesions. The pathologic
Figure 2. A, Histologically, the lesion forms a lobulated mass of proliferating connective tissue containing many multinuclear giant cells (hematoxylin-eosin stain, original magnification ×100). B, Histochemical staining for tartrate-resistant acid phosphatase demonstrating a uniform reactivity in the cytoplasm of the multinuclear giant cells, with only scattered reactivity in the mononuclear cells (TRAP staining, original magnification ×100). C, Multinuclear giant cells in the lesion show a strong reactivity for CD68, with some of the mononuclear cells also exhibiting a moderate reactivity (immunocytochemical staining, original magnification ×100). D, Ki-67-positive nuclear staining is seen almost exclusively in the mononuclear cells, with the giant cells showing no reactivity (immunocytochemical staining, original magnification ×150).

Figure 3. A, The adherent multinuclear giant cells (arrows) isolated from the lesion are seen on the coverslips after 1 hour of culture (phase-contrast photomicrograph, original magnification ×150). B, When cocultured with the bovine cortical bone ground slices, the multinuclear giant cells could excavate resorption lacuna (arrows) on the bone surface (phase-contrast photomicrograph, original magnification ×200).
evaluation of the present case suggested the lesion to be GCG. Central giant cell lesions of the skull may provide unique challenges to complete surgical excision because of the number and complexity of vital structures in this region. Although the lytic lesion of the present case caused marked destruction of the temporal bone, the underlying dura mater and the adjacent TMJ/auditory structures were not involved. Thus, the lesion was removed by careful curettage. Postoperative radiation therapy was not applied mainly because of the concern of its potential for sarcomatous transformation. The patient was monitored regularly after the operation and the fact that he was free of the disease for 26 months lends support to the diagnosis of GCG.

The origin of MGCs in GCG has long been a matter of considerable interest. A number of possible cells of origin for the MGCs have been proposed. The immunoreactivity with the histiocytic markers AAT, AACT, lysozyme and CD68 in the MGCs in both GCG and GCT provided evidence for a histocyte/macrophage origin.6,7 Alternatively, the MGCs in giant cell lesions have been thought to resemble or to be identical to osteoclasts because of the similarity in their morphology and the presence of abundant acid phosphatase and other hydrolytic enzymes, osteoclast-specific cellular antigens, and receptors for calcitonin, a phenotypic marker of osteoclasts. In the current study, our immunocytochemical findings were similar to those presented by others and suggest that MGCs in GCG possess histocyte/macrophage characteristics. Concomitantly, we also demonstrated the presence of TRAP activity, an osteoclast-specific enzyme activity, in the MGCs of the lesion. Furthermore, the MGCs isolated from the lesion showed the characteristic appearance of osteoclasts and possessed the ability to excavate the surface of bone slices in vitro. Based on these findings and those of others, it appears that MGCs in the giant cell lesions cannot be accurately classified as either macrophages or as osteoclasts. Rather, they may represent a related precursor cell population that has not committed to either adult phenotype, but that possesses features of both macrophages and osteoclasts. This concept may help to explain some of the clinical and experimental findings of these cells, namely their ability to resorb bone and to engulf red blood cells and hemosiderin deposits. In fact, osteoclasts are now believed to derive from hematopoietic cells of monocyte/macrophage lineage,9 which may also help to explain the morphologic and functional overlap between the MGCs of GCG and macrophages/osteoclasts.

Recently, the focus of study of giant cell lesions has shifted from the giant cells to the mononuclear cells. Many investigators believe that the mononuclear cells are the proliferative cell elements responsible for the biologic activity of giant cell lesions.10 This was supported by our observation that the immunoreactivity for Ki-67 was exclusively detected in mononuclear cells of the lesion. We also found that some of the mononuclear cells exhibited almost identical immunocytochemical (CD68, AAT, AACT, and lysozyme) and histochemical (TRAP) reactivity as the MGCs in the lesion. This subpopulation of the mononuclear stromal cells may represent precursors of the MGCs and coalescence or fusion of these precursor cells could result in giant cell formation.

References