Central Giant Cell Lesion

James C. Valentine · Brenda L. Nelson

Received: 2 August 2011 / Accepted: 24 August 2011 / Published online: 4 September 2011
© Springer Science+Business Media, LLC 2011

Abstract A classic case of central giant cell lesion (CGCL) is presented with emphasis on clinical, radiologic, and histologic features. The differential is discussed including peripheral giant cell granuloma, brown tumor of hyperparathyroidism, and giant cell tumor of bone. The molecular pathway of osteoclastogenesis is selectively reviewed and applied to suggest possible etiologies of the giant cell lesions. CGCL syndromes and treatment are also discussed.

Keywords Central giant cell lesion · Giant cell reparative granuloma · Osteoclast · Giant cell · RANK · RANKL · NFAT · NFATc1 · SH3BP2 · Peripheral giant cell granuloma · Giant cell tumor of bone · Brown tumor of hyperparathyroidism · Osteitis fibrosa cystica

History

A 20-year-old female presented to her general dentist with a chief complaint of painless swelling of her lower left jaw. The patient noticed the swelling only 1 week prior and denied a history of recent trauma or infection. Intraoral exam revealed an expansion of the left mandibular alveolar ridge.

Disclaimer: The opinions and assertions expressed herein are those of the author and are not to be construed as official or representing the views of the Department of the Navy or the Department of Defense.

J. C. Valentine (✉) · B. L. Nelson
Department of Anatomic Pathology, Naval Medical Center
San Diego, 34800 Bob Wilson Drive, San Diego,
CA 92134-5000, USA
e-mail: james.valentine@med.navy.mil

Radiography

Panographic radiograph showed a well-circumscribed multilocular radiolucent lesion of the left posterior mandible. The defect was delineated with no obvious cortical expansion, but showed definitive communication with the oral cavity. The mandibular second molar was notable for resorption of the distal root (Fig. 1).

Diagnosis

The patient underwent incisional biopsy. Hematoxylin and eosin stained sections revealed a proliferation of multinucleated giant cells (MGCs) within a fibrous stroma focally surfaced by epithelium (Fig. 2). The stroma contained plump spindle-shaped cells with abundant wispy pink cytoplasm, smooth oval nuclei, finely granular chromatin, and punctuate nucleoli. Areas of hemorrhage and hemosiderin deposition were readily identified. Scattered chronic inflammatory cells consisted primarily of macrophages and lymphocytes. Mitotic figures were not uncommon. The MGCs had granular amphophilic cytoplasm and between five and thirty nuclei. Occasional apoptotic debris was identified, but necrosis was absent. Osteoid deposition was minimal. Lastly, the specimen was focally surfaced by epithelium; however, clinical and radiologic correlation determined the origin of the lesion to be intraosseous (Fig. 3).

Discussion

Central giant cell lesion (CGCL) likely represents a benign neoplasm [1], though its former designation, reparative

Fig. 1 Panoramic radiograph shows a well-circumscribed multilocular radiolucent lesion of the left posterior mandible with molar resorption

giant cell granuloma, reflects the theory that it may be a reactive lesion. CGCLs are frequently discovered incidentally on routine dental radiography. A minority of patients experience symptoms, such as swelling, pain, paresthesia, or perforation of the cortical bone resulting in ulceration and oral communication. The age range for those affected is broad, although most occur in patients younger than thirty [2]. Women are affected more frequently than men, and high estrogen states, such as pregnancy, have been implicated in CGCL proliferation. Lesions rarely express estrogen receptors, however [3].

Fig. 2 A high-power view shows plump, spindled mononuclear cells and multinucleated giant cells. The nuclear morphology between these cell types is similar. Abundant vascular spaces contain erythrocytes

Fig. 3 A low-power view shows osteoclast-like giant cells evenly distributed within the stroma. Mucosa overlies the lesion where it has perforated the cortical bone

The anterior mandible is commonly affected and the lesion frequently crosses the midline. Extra-gnathic incidence is rare [2].

Radiographically, CGCL is a well-defined, non-corticated radiolucency. The smallest lesions can be unilocular, but most CGCLs are loculated by undulating septae. Admixed radiopacities are rare [4]. Rapid growth, cortical plate perforation, and root resorption suggest more aggressive behavior [5].

Histologically, CGCL is composed of osteoclast-like giant cells grouped or dispersed amongst spindled mononuclear cells with abundant pink cytoplasm. Hemorrhage, hemosiderin, collagen bundles, metaplastic ossification, mixed inflammation, and mitotic activity are common. Plasma cells are purported to be rare [2], though they are abundant in this example. Clinical and radiographic correlation is required to rule out a peripheral giant cell granuloma (PGCG), which may cause “cupping” of the underlying bone, but should not destroy bone.

Central giant cell lesion may arise sporadically or in association with Cherubism, Noonan Syndrome, Jaffe-Campanacci Syndrome, Neurofibromatosis type 1, or Ramon Syndrome [6, 7]. The differential diagnosis of CGCL includes the so-called “brown tumor of hyperparathyroidism” (BTOH), PGCG, and giant cell tumor of bone (GCTB). Clinical correlation is always required to distinguish these lesions because their histologic appearance overlaps. A review of physiologic osteoclast signaling provides a useful framework to conceptualize the likely histogenesis of these related giant cell lesions.

In a simplified overview of osteoclastogenesis (Fig. 4), bone marrow-derived osteoclast-precursor cells are committed to osteoclastic differentiation by intranuclear buildup of NFATc1 (nuclear factor of activated T cells) [8].

Fig. 4 In a simplified overview of osteoclastogenesis, PTH increases osteoblastic RANKL expression. RANKL stimulates RANK on osteoclast precursors, increasing intranuclear NFATc1. SH3BP2 also increases NFATc1. NFATc1 commits the precursor cell to osteoclastic differentiation. CGCL, PGCG, and BTOH consist of cells that mimic osteoclasts and osteoclast precursors. GCTB consists of these two cell populations and a third population that mimics osteoblasts

NFATc1 is amplified both by the presence of SH3BP2 protein [9] and by stimulation of RANK (receptor activator of NF- κ B), which is expressed on the osteoclast-precursor cell surface. RANK is stimulated by the RANK ligand (RANKL), which is expressed by osteoblasts. Osteoblastic RANKL expression is in turn stimulated by parathyroid hormone (PTH). Thus, the end result of PTH secretion is osteoclast proliferation, bone resorption, and calcium liberation. Pathologically sustained PTH elevation causes BTOH, which consists of mononuclear osteoclast-precursors and multinucleated differentiated osteoclasts.

The other giant cell lesions may also represent pathologic variations of osteoclastogenesis, though their mechanisms are less well understood. CGCL and PGCG are composed of mononuclear stromal cells that mimic osteoclast-precursors and MGCs that mimic differentiated osteoclasts [10]. NFATc1 expression is also increased in both of these lesions [11]. They differ, however, in that CGCL arises centrally within bone, while PGCG is a gingival soft tissue lesion. The bilateral CGCLs of Cherubism are caused by an activating germline mutation of the SH3BP2 gene (chromosome 4p16.3). Sporadic SH3BP2 mutations have been identified in CGCL, but not in PGCG [12].

In addition to osteoclast-precursor-like cells and osteoclast-like giant cells, GCTB contains a third cell type that mimics RANKL-expressing osteoblasts. It is postulated that the osteoblast-like cells are the sole neoplastic cells of GCTB, and that these neoplastic cells recruit osteoclast-precursors and osteoclastic giant cells [13]. Osteoblast-like cells have not been described in CGCL and PGCG. Future investigation may determine if this cell population is responsible for the metastatic potential of GCTB, and if its absence restricts CGCL and PGCG from metastasis.

Clinical differentiation of CGCL and GCTB is often straightforward because CGCL usually arises in the gnathic bones and GCTB usually arises in long bone metaphyses. The differential remains challenging, however, in rare cases of giant cell lesions arising in the sphenotemporal bones. Some authors claim that GCTB and CGCL can be distinguished morphologically [14], some envision a spectrum of disease [15], and others neglect the incidence of craniofacial GCTB altogether [13, 16]. As investigators elucidate the pathologic molecular signaling in giant cell lesions, molecular testing may enable more accurate classification.

Molecular testing may also provide prognostic data for giant cell lesions, whose behavior is currently difficult to predict. Nonaggressive CGCLs grow slowly and painlessly, respecting the adjacent teeth and cortical bone. They are usually treated with curettage and approximately 20% will recur. Aggressive CGCLs grow rapidly, perforate the gnathic bone cortex, resorb the roots of adjacent teeth and grossly deform the face. Only *en bloc* resection provides a chance of surgical cure in aggressive cases. To minimize risk of poor esthetic or functional outcome, many clinicians treat aggressive CGCLs with intralesional triamcinolone, intranasal calcitonin, or subcutaneous interferon alfa-2a. Radiation therapy and other chemotherapeutic agents such as methotrexate, doxorubicin, and cyclophosphamide have also been employed [15].

References

1. Amaral FR. Clonality analysis of giant cell lesions of the jaws. *Braz Dent J*. 2010;21(4):361–4.
2. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. World health organization classification of tumours: head and neck tumours. Lyon: IARC Press; 2005.
3. Whitaker BS. Estrogen and progesterone receptor status of central giant cell lesions of the jaws. *Oral Surg Oral Med Oral Pathol*. 1994;77(6):641–4.
4. Stavropoulos F, Katz J. Central giant cell granulomas: a systematic review of the radiographic characteristics with the addition of 20 new cases. *Dentomaxillofac Radiol*. 2002;31(4):213–7.
5. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. A clinical, radiologic, and histopathologic study. *Oral Surg Oral Med Oral Pathol*. 1993;75(2):199–208.
6. Edwards PC. Bilateral central giant cell granulomas of the mandible in an 8-year-old girl with Noonan syndrome (Noonan-like/multiple giant cell lesion syndrome). *Oral Surg Oral Med Oral Pathol*. 2005;99:334–40.
7. Dunlap C. The Noonan syndrome/cherubism association. *Oral Surg Oral Med Oral Pathol*. 1989;67(6):698–705.
8. Aeschlimann D. The vital osteoclast: how is it regulated? *Cell Death Differ*. 2004;11:S5–7.
9. Lietman SA, Yin L, Levine MA. SH3BP2 is an activator of NFAT activity and osteoclastogenesis. *Biochem Biophys Res Commun*. 2008;371(4):644–8.

10. Liu B, Yu SF, Li TJ. Multinucleated giant cells in various forms of giant cell containing lesions of the jaws express features of osteoclasts. *J Oral Pathol Med*. 2003;32(6):367–75.
11. Amaral FR. NFATc1 and TNFalpha expression in giant cell lesions of the jaws. *J Oral Pathol Med*. 2010;39(3):269–74.
12. Carvalho VM. Novel mutations in the SH3BP2 gene associated with sporadic central giant cell lesions and cherubism. *Oral Dis*. 2009;15(1):106–10.
13. Werner M. Giant cell tumor of bone: morphological, biological, and histogenetical aspects. *Int Orthop*. 2006;30:484.
14. Bertoni F, et al. Giant cell tumor of the skull. *Cancer*. 1992;70:1124–32.
15. Saw S, et al. Giant cell tumour and central giant cell reparative granuloma of the skull: do these represent ends of a spectrum? A case report and literature review. *Pathol Oncol Res*. 2009;15(2): 291–5.
16. Fletcher CDM, Unni KK, Mertens F, editors. World health organization classification of tumours: tumors of soft tissue and bone. Lyon: IARC Press; 2002.