Studies of Cell Cycle-associated Proteins in a Case of Giant Cell Granuloma of Mandible

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Abstract

Central Giant Cell Granuloma (CGCG) is a localized benign osteolytic lesion with variably aggressive nature. Due to the rarity of this disease, only a few studies with a limited number of cases have been reported, the results of which are controversial. Hence, there is not much data on the possible mechanisms underlying its aggressive biological behavior. In our study, immunohistochemistry was performed on a 50-year old female diagnosed with a giant cell granuloma of the mandible. We attempted to examine the expression profile and cellular distribution of cell cycle-associated proteins: cyclin D1, p53, PCNA, MIB-1 and facor XIIIa. Our results demonstrated that high-level expression of cyclin D1 was predominant in the nuclei of 85% of giant cells whereas cyclin D1 staining was noticed in only 20% of mononuclear cells. Expression of PCNA and MIB-1, on the other hand, was observed in 70% and 40% of mononuclear cells respectively, with less than 10% positive staining present in the giant cells. P53 protein did not appear to be over-expressed in either mononuclear or giant cells, and factor XIIIa was detected only in isolated stromal fibroblasts. These results support the hypothesis that over-expression of cyclin D1 in giant cells may play a role in the pathogenesis of CGCG, and the differential expression pattern of cyclin D1 and PCNA may be involved in the formation of multinucleated giant cells.

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Introduction

Central giant cell granuloma (CGCG) is a rare bony lesion that usually affects the maxilla, mandible and occasionally cranial bones. It is characterized by the proliferation of fibroblasts and multinucleated giant cells arising from the mononuclear cells that express markers for both macrophages and osteoclasts.[1-3] Although considered benign, CGCG often exhibits an aggressive clinical course and has a potential for extensive bony destruction, recurrence and even metastasis. [4-5] CGCG accounts for less than 7% of all benign lesions in teeth-bearing areas of the mandible and maxilla. CGCG affects both children and adults with higher frequency in female. The lesion is more commonly seen in people in their fourth and fifth decades. Although its etiology is unclear, it has been suggested that CGCG can be triggered by trauma or inflammation.[6-8]

Recent studies have shown alteration of several cell cycle regulatory protein expressions in both central and peripheral giant cell lesions.[9-11] In addition, tumor cells in these lesions display a relatively high proliferation index, particularly in mononuclear cells.[12-15] The precise pathogenesis and histogenesis of CGCG, however, remains unclear. The objective of this study is to investigate the expression profile of cell cycle-related protein in a case of mandible giant cell granuloma.

Report of Case

A 50-year old white female with a mass on her right lower mandible presents in the Oral and Maxillofacial Department. This lesion was noticed shortly after a dental cleaning approximately one year ago. She was initially treated for an abscess with antibiotics over the course of the previous year and root canal was also performed with no resolution. The mass became progressively larger and was complicated by frequent bleeding. Laboratory work-ups including hematologic, metabolic panels, and liver function were all within normal limits. Radiographic finding suggested an

osteolytic lesion, and possible CGCG. The patient then underwent marginal mandibular resection of the right jaw with peripheral ostectomy, plus removal of teeth #31, 30, 29 and 28, with peripheral ostectomy and curettage of the remaining mandibular bone at Buffalo General Hospital, Buffalo, New York.

Pathologic Findings

The soft tissue portion of the specimen consists of a 2 x 2.5 x 1.5 cm. irregular mass, brown-red in color with focal hyperemic changes on its cut surface. Microscopic examination of the hematoxylin-eosin stained section reveals that the lesion predominantly consists of abundant round to spindle-shaped mesenchymal cells admixed with dilated hyperemic capillaries and hemosiderin pigment granules (Fig 1A). Numerous multinucleated giant cells (osteoclast-like) are present in the background of mononuclear fibrohistiocytes, red blood cells and scattered chronic inflammatory cells. These giant cells display multiple oval to round vesicular nuclei with inconspicuous nucleoli. The morphological features of these nuclei are similar to those of surrounding mononuclear cells (Fig 1B). Mitotic figures are rare. Furthermore, immunohistochemistry studies demonstrate a high-level expression of cyclin D1, predominantly in the nuclei of 85% of giant cells whereas cyclin D1 staining was noticed in only 20% of mononuclear cells (Fig 2A and 2B). Expression of PCNA and MIB-1, on the other hand, was observed in 70% and 40% of mononuclear cells respectively, with less than 10% positive staining present in the giant cells (Fig 3A and 3B). P53 protein did not appear to be over-expressed in either mononuclear or giant cells, and factor XIIIa was detected only in isolated stromal fibroblasts.

Summary

CGCG is considered a benign but locally aggressive neoplasm that is uncommon in the head and neck region. The pathogenesis and histogenesis of this lesion is unclear. In our case study, the immunoprofile of some cell cycle-associated protein was examined, particularly on the multinucleated giant cells and mononuclear cells. Our results suggest that overexpression of cyclin D1 in giant cells may play a role in the pathogenesis of CGCG, and the differential expression pattern of cyclin D1 and PCNA may be involved in the formation of multinucleated giant cells.

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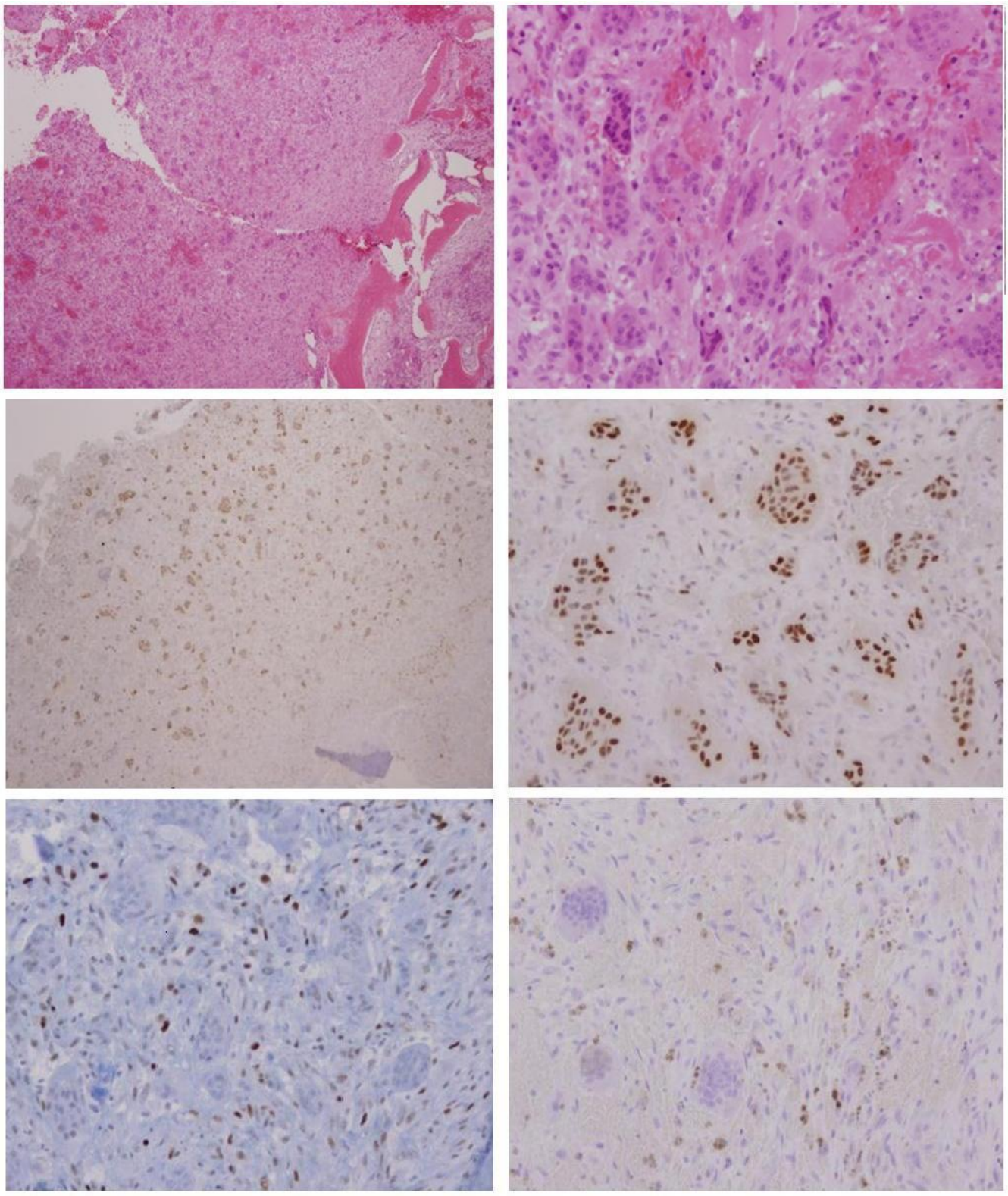

1A	1B
2A	2B
3A	3B

Figure 1. Nests of osteoclasts-like giant cells admix with oval and spindle-shaped mononuclear stromal cells in the background of numerous dilated hyperemic capillaries. Scattered hemosiderin granules are also noted. **A,** original magnification x40; **B,** x200.

Figure 2. Higher nuclear expression level of Cyclin D1 was observed in giant cells (85% positive staining) than that of surrounding mononuclear cells (20% positive staining). **A,** original magnification x40; **B,** x200.

Figure 3. Expression of PCNA (**A,** original magnification x200) and MIB-1 (**B,** original magnification x200) was observed predominantly in mononuclear cells with positive staining of 70% and 40%, respectively, versus only 10% in giant cells.