PATHOLOGY

Genetic Analysis of Giant Cell Lesions of the Maxillofacial and Axial/Appendicular Skeletons

Zachary S. Peacock, DMD, MD, [*] *Joseph H. Schwab, MD,* [†] *William C. Faquin, MD, PhD,* [‡] *Francis J. Hornicek, MD, PhD,* [§] *Yair Benita, PhD,* [‖] *David H. Ebb, MD,* [¶] *and Leonard B. Kaban, DMD, MD* [#]

Purpose: To compare the genetic and protein expression of giant cell lesions (GCLs) of the maxillofacial (MF) and axial/appendicular (AA) skeletons. We hypothesized that when grouped according to biologic behavior and not simply by location, MF and AA GCLs would exhibit common genetic characteristics.

Materials and Methods: This was a prospective and retrospective study of patients with GCLs treated at Massachusetts General Hospital from 1993 to 2008. In a preliminary prospective study, fresh tissue from 6 aggressive tumors each from the MF and AA skeletons (n = 12 tumors) was obtained. RNA was extracted and amplified from giant cells (GCs) and stromal cells first separated by laser capture microdissection. Genes highly expressed by GCs and stroma at both locations were determined using an Affymetrix GeneChip analysis. As confirmation, a tissue microarray (TMA) was created retrospectively from representative tissue of preserved pathologic specimens to assess the protein expression of the commonly expressed genes found in the prospective study. Quantification of immunohistochemical staining of MF and AA lesions was performed using Aperio image analysis to determine whether immunoreactivity was predictive of aggressive or nonaggressive behavior.

Results: Five highly ranked genes were found commonly in GCs and stroma at each location: matrix metalloproteinase-9 (MMP-9), cathepsin K (CTSK), T-cell immune regulator-1 (TCIRG1), C-type lectin domain family-11, and zinc finger protein-836. MF (n = 40; 32 aggressive) and AA (n = 48; 28 aggressive) paraffin-embedded tumors were included in the TMA. The proteins CTSK, MMP-9, and TCIRG1 were confirmed to have abundant expression within both MF and AA lesions. Only the staining levels for TCIRG1 within the GCs predicted the clinical behavior of the MF lesions.

[*]Assistant Professor, Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital and Harvard School of Dental Medicine, Boston, MA.

[†]Assistant Professor, Department of Orthopaedics, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

[‡]Associate Professor, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

[§]Associate Professor, Department of Orthopaedics, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

[‖]Former Fellow, Center for Computational and Integrative Biology, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

[¶]Assistant Professor, Department of Pediatrics, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

[#]Walter Guralnik Distinguished Professor, Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital and Harvard School of Dental Medicine, Boston, MA.

The present study was supported by the Department of Oral and Maxillofacial Surgery Education and Research Fund and the Department of Orthopaedic Surgery, Massachusetts General Hospital and Harvard School of Dental Medicine, Boston, MA.

Z.S.P. and J.H.S. are co-first authors.

This study was presented at the Surgical Forum at the Annual Meeting of the American College of Surgeons, October 2014, San Francisco, CA, and published as an abstract in a supplement of the Journal of American College of Surgeons (Peacock ZS, Schwab JH, Faquin WC, et al: Genetic analysis of giant cell tumors of the maxillofacial and axial/appendicular skeleton. J Am Coll Surg 219:S70, 2014).

Address correspondence and reprint requests to Dr Peacock: Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Warren 1201, 55 Fruit Street, Boston, MA 02114; e-mail: zpeacock@partners.org

Received May 27 2016

Accepted July 19 2016

0278-2391/16/30618-8

http://dx.doi.org/10.1016/j.joms.2016.07.014

Conclusions: MMP-9, CTSK, and TCIRG1 are commonly expressed by GCLs of the MF and AA skeletons. This supports the hypothesis that these lesions are similar but at different locations. TCIRG1 has not been previously associated with GCLs and could be a potential target for molecular diagnosis and/or therapy.

J Oral Maxillofac Surg ■*:1-11, 2016*

Giant cell lesions (GCLs) are intraosseous benign tumors containing multinucleated giant cells (GCs) within a mononuclear stroma. They can affect both the maxillofacial (MF) and the axial/appendicular (AA) skeletons. Lesions at both sites can vary from small, slow-growing tumors recognized as incidental radiographic findings to large destructive lesions, leading to displacement or resorption of adjacent structures or pathologic fracture.[1,2]

GCLs of the MF skeleton are more common in females and younger patients (2:1 females to males during the first and second decade) compared with those of the AA skeleton (1.3 to 1.5 females to males during the third to fifth decade).[3-9] MF GCLs are more likely to be asymptomatic, and they are often discovered on routine dental radiographic examinations.[4,10]

Controversy remains regarding the biologic relationship between GCLs of the jaws and giant cell tumors (GCTs) in the AA skeleton.[3-5,10-14] This is because subgroups of these tumors (ie, aggressive and nonaggressive) according to biologic behavior have not been differentiated in reported comparisons. Some investigators have postulated that MF and AA GCLs are distinctly separate lesions because of differences in clinical behavior and histopathologic features.[3,11,15] Others have supported the hypothesis that these are similar lesions in different locations representing a continuum of the same disease process.[3-5,16,17] In each location, the pathogenesis has been hypothesized to involve stromal fibroblasts that recruit monocytes, which then transform into multinucleated GCs.[18,19] These GCs have been shown to be phenotypically osteoclasts through immunohistochemistry.[20]

Clinical and radiographic features can be used to classify GCLs in both locations as aggressive or nonaggressive.[5,10,21] Lesions of the MF region are considered aggressive if they are larger than 5 cm, recurrent, or meet 3 of the following 5 criteria: rapid growth, root resorption, tooth displacement, cortical bone thinning, and/or perforation. Nonaggressive lesions grow slowly and are asymptomatic, with a low rate of recurrence after enucleation or curettage. AA lesions are classified according to the classification system of Enneking, also by clinical and radiographic behavior.[1,22] Enneking stage 1 (latent) refers to static lesions or those that heal spontaneously. Stage 2 (active) tumors exhibit progressive growth but are limited by natural barriers (ie, cortices). Stage 3 lesions are locally aggressive, with destruction of natural barriers.[22] As previously outlined, both the Enneking and the Chuong and Kaban[21] MF classification systems, using clinical and radiographic criteria, can be modified to produce a single, biologically consistent binary classification for GCTs in both locations: aggressive and nonaggressive.[1,12,13]

Studies comparing GCLs of the MF and AA skeletons have been limited by inconsistent terminology, and investigators have typically grouped all lesions together, without considering the clinical or biologic behavior. MF GCLs were first referred to as "giant cell reparative granuloma" by Jaffe[11] in 1953. Reports of spontaneous resolution have been published.[23,24] However, other MF GCLs are destructive and grow rapidly.[10] Additionally, the reluctance to label MF GCLs as "giant cell tumors" can result from the reports of metastases and malignant transformation from AA GCLs.[25-27] However, retrospective analyses of cases of lung metastases from AA GCTs have indicated that these might actually be malignant tumors that happen to contain GCs.[28] In a recent study, investigators found consistent mutations in histone 3.3 driver variants (*H3F3A* gene) in the stromal cells of AA GCLs.[29] They reported H3.3, H3F3A, and H3F3B in a variety of bone and cartilage tumors.[29,30] A subsequent study by a different group of both aggressive and nonaggressive GCLs of the MF skeleton did not find these specific mutations.[31] Although this supports that these are different lesions, mutations in histone, the protein that packages DNA into nucleosomes, have been found in a variety of bone and cartilage tumors and in pediatric brain tumors and might not be involved in pathogenesis.[32-34]

Our group has previously compared the lesions in each location by biologic behavior using the Chuong and Kaban classification[21] and a modified version of the Enneking classification[1] (ie, aggressive or nonaggressive) and found the lesions to be similar with regard to the phenotypic, clinical, and radiographic appearance.[13] Subsequently, it was shown that these lesions are histologically similar and that they could not be differentiated consistently by blinded pathologists.[14] These findings support the conclusion that they are similar tumors in different locations.