

## Osteoclast-like Giant Cell Tumor of the Parotid Gland Accompanied with Carcinoma ex Pleomorphic Adenoma

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The origin of osteoclast-like giant cell tumor (OGCT) of the salivary gland has been debated because the prototypic cells of osteoclast-like cells and mononuclear stromal cells are largely unexplained in this gland. Bone marrow-derived CD14+ and CD45+ monocyte-derived multipotential cells (CD14+/CD45+ MOMC) may be one of the possible origins of OGCTs of salivary glands, which have never been explored in salivary OGCTs. We present a case of OGCT accompanied with carcinoma ex pleomorphic adenoma in the parotid gland of a 67-year-old Korean female. The tumor presented as a rapidly growing cervical mass comprising a central area of carcinoma ex pleomorphic adenoma and a peripheral circumferential area of OGCT. The immunohistochemical staining pattern was phenotypically consistent with bone marrow-derived CD14+/CD45+ MOMC. This case is the first report of a salivary OGCT in Korea.

**Key Words:** Giant cell tumor; Parotid gland; Mixed tumor, malignant; Osteoclasts; Monocytes

Osteoclast-like giant cell tumor (OGCT) of the salivary gland is a rare entity, first described in 1984.<sup>1</sup> OGCT comprises osteoclast-like giant cells (OGCs) and mononuclear stromal cells (MNCs) similar to those seen in giant cell tumors (GCTs) of the bone. The reason why OGCT is morphologically similar to GCT of bone arising in the salivary gland has been unclear. Hence, the origin of OGCs and MNCs has been debated for a long time and the exact origin of OGCT remains unclear. Bone marrow-derived CD14+ and CD45+ monocytes may be one of the possible origins based on the previous studies of GCTs and OGCTs of other organs, but salivary OGCT has not been explored.<sup>1</sup> Circulating CD14+ and CD45+ monocytes originate from hematopoietic stem cells in the bone marrow and comprise 5-10% of circulating white blood cells in humans.<sup>2</sup> These prototype cells are capable of differentiating into various cell types, including phagocytes termed CD14+ and CD45+ monocyte-derived multipotential cells (CD14+/CD45+ MOMCs).<sup>2</sup> MOMCs have a unique phenotype positive for hematopoietic and monocytic

lineage markers (CD14, CD33, CD45, and CD68), stem cell markers (CD34 and CD105) and mesenchymal markers (fibronectin and vimentin), but they do not express CD117/c-kit and CD133.<sup>3</sup> These findings clearly show that CD14+/CD45+ MOMCs have mixed morphological and phenotypical features of phagocytes and mesenchymal cells.<sup>2</sup>

We report a case of OGCT with adenocarcinoma ex pleomorphic adenoma in the parotid gland exhibiting a phenotype similarity to that of CD14+/CD45+ MOMC and discuss the possible pathogenesis of salivary OGCT.

### CASE REPORT

A 67-year-old woman presenting with a rapidly growing neck mass and facial nerve palsy was referred to our hospital. The patient had undergone medical therapy 2 months previously, but the mass was intractable. The patient experienced weight loss

of approximately 3 kg in 2 months. Neck ultrasonography showed an irregularly margined, low echoic mass with inner calcification, which was suggestive of malignancy. The patient underwent a right total parotidectomy and modified right neck lymph node dissection type III. On follow-up, the patient 2 months later after an operation for pulmonary insufficiency. An autopsy was not performed.

The resected right parotid gland measured  $7 \times 5 \times 2.5$  cm and the cut surface revealed a well-demarcated mass measuring  $4 \times 3.5 \times 3$  cm, which comprised a central pinkish-gray firm myxoid area and a peripheral circumferential darkish tan-brown soft area (Fig. 1A). The central firm area, measuring  $2 \times 1.5$  cm, was admixed with calcification, and the peripheral portion, measuring 1.5 cm in thickness, was variegated with hemorrhage. On microscopic examination, the central area was revealed to be pleomorphic adenoma (Fig. 1B), and foci of cribriform and tubular structures of large, pleomorphic, and hyperchromatic nuclei and atypical mitoses with necrosis (Fig. 1C). The peripheral surrounding area of the mass was composed of two cell populations: numerous MNCs among which conspicuous OGCs were evenly distributed (Fig. 1D). The MNCs were variable in size and occasionally spindle- or oval-shaped, and large numbers of nuclei were hyperchromatic. The OGCs had central, bland-appearing nuclei that averaged 10 in number but ranged to over 30 with prominent nucleoli; the cytoplasm frequently contained vacuoles. Mitotic counts of up to 8 were observed in 10 high-power fields in MNCs, but this was not evident in OGCs. The observed histological morphologies were consistent with those of OGCT. The central area of the mass was diagnosed as carcinoma ex pleomorphic adenoma and distinctly delineated from OGCT (Fig. 1E). The OGCT area was larger (up to 60%) than carcinoma ex pleomorphic adenoma (up to 40%). Lymph node metastasis was not found.

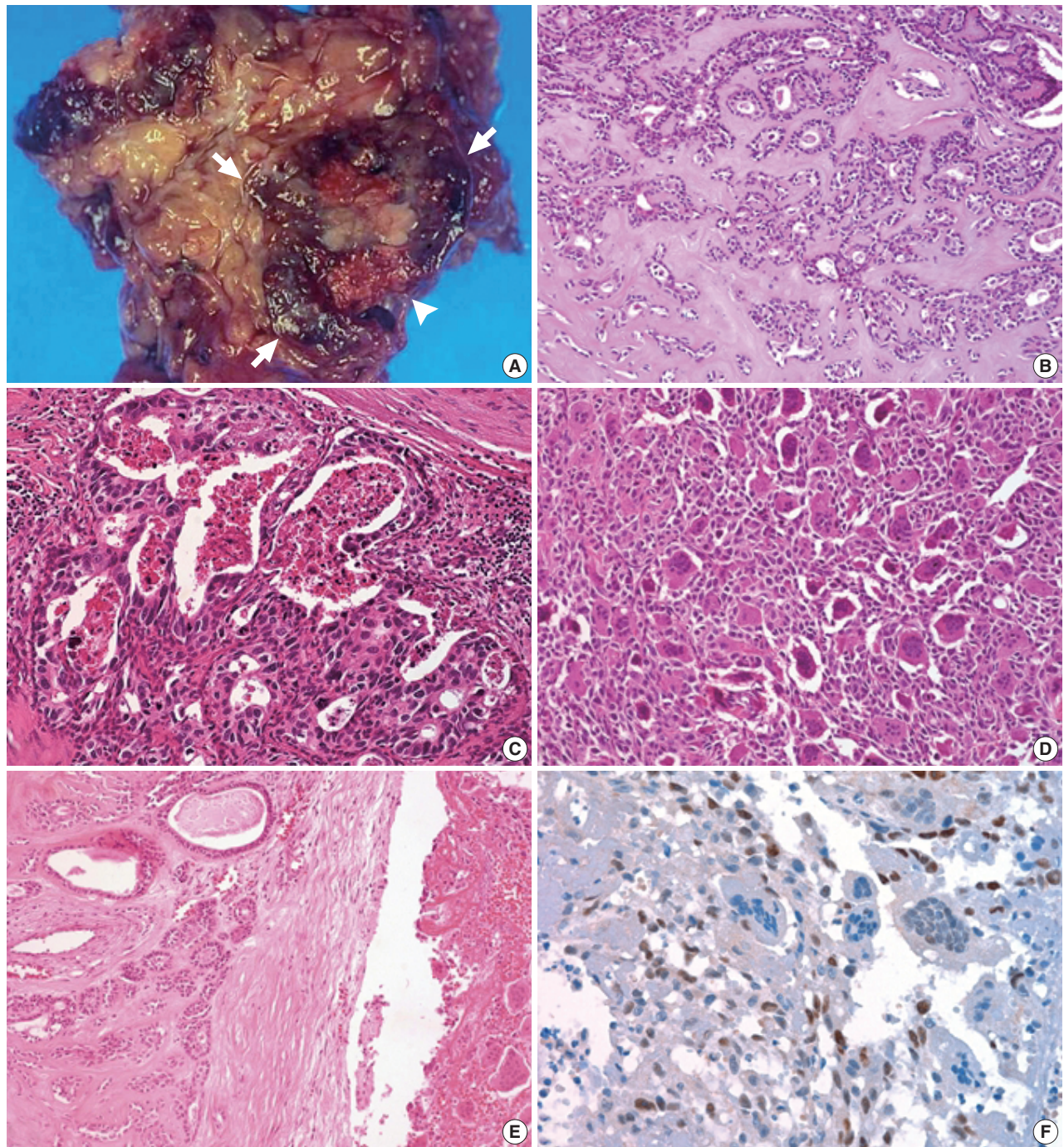
We characterized the cellular components of OGCT by immunostaining with hematopoietic and monocytic lineage markers (CD14, CD33, CD45, CD68, and  $\alpha 1$ -antitrypsin [AAT]), stem cell markers (CD34 and CD117), mesenchymal markers (fibronectin and vimentin), epithelial markers (CAM5.2, cytokeratin [CK]5/6, CK7, CK19, and epithelial membrane antigen [EMA]), and myoepithelial markers (calponin, S-100, and smooth muscle actin [SMA]).<sup>4</sup> Many MNCs were positive for a panel of MOMC markers (CD14, CD33, CD45, CD68, CD34, vimentin, and fibronectin), AAT, and p53 antigen (Fig. 1F). Many OGCs were positive for CD33, CD68, vimentin, fibronectin, and AAT. CD117 was negative in both MNCs and OGCs (Fig. 2). Some MNCs and OGCs were positive for myoepitheli-

al markers (S-100). Epithelial markers (CK7, EMA, CAM5.2, CK5/6, and CK19) were negative in both MNCs and OGCs. The carcinoma expressed epithelial markers (CAM5.2, CK5/6, CK7, CK19, and EMA) and p53 antigen, and the pleomorphic adenoma was positive for epithelial (CAM5.2, CK5/6, CK7, CK19, and EMA) and myoepithelial (calponin, S-100, and SMA) markers.

## DISCUSSION

This is the first Korean case of OGCT accompanied with carcinoma ex pleomorphic adenoma of the parotid gland. A total of 17 cases have been reported worldwide and most of them have occurred in western countries.<sup>5-14</sup> Salivary OGCT can be divided into two groups: OGCTs accompanied with carcinoma ex pleomorphic adenoma and pure OGCTs. In the former case, the tumors typically comprise the OGCT as the major (60-95%) component with carcinoma forming the minor (5-40%) component.<sup>9,11,13-15</sup> In the present case, the tumor was composed of 60% OGCT and epithelial component of 40%. The two components tend to be relatively well-defined in the center of the interface, rather than diffusely intermixed.<sup>5,8,9,11,14,15</sup> The tumors of this group may undergo perineural invasion,<sup>14</sup> local recurrence, and distant metastasis,<sup>5,9</sup> and show poor survival outcomes. In contrast, all the MNCs and OGCs of pure OGCTs have bland-appearing nuclei, and the prognosis is favorable.

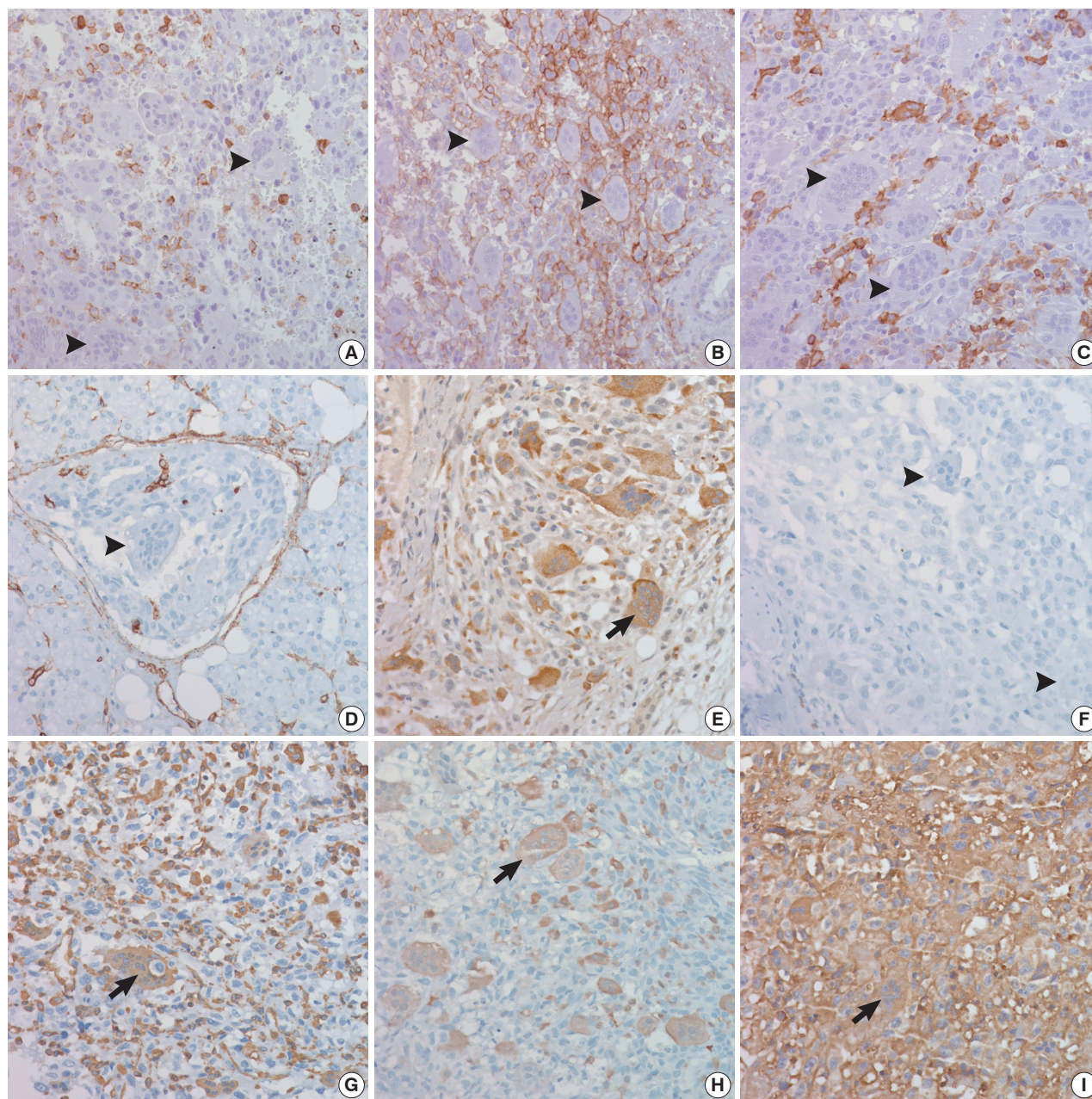
The reason why OGCTs morphologically similar to giant cell tumor of bone arise in the salivary gland is unclear. There have been many suggestions on the origin of MNCs in salivary OGCTs. Eusebi *et al.*<sup>8</sup> considered MNCs to be of epithelial origin because they observed a transition site from the carcinomatous component to MNC on light microscopic examination. However, they concluded that the existence of a transition site was highly subjective and that there was no convincing evidence of epithelial or myoepithelial origin from the results of electron microscopic examination and immunohistochemical studies. The myoepithelial origin was once proposed in view of the fact that the majority of extraskeletal OGCTs manifested in exocrine organs such as the pancreas, liver, breast, thyroid, and salivary gland, but myoepithelial evidence has never been found.<sup>16</sup> Tse *et al.*<sup>14</sup> suggested that salivary OGCT was possibly an undifferentiated carcinoma, demonstrating that OGCT and the accompanying salivary duct carcinoma shared the mutation of the same allele on Chr17p13, and MNCs were positive for epithelial markers (CKAE1/3, EMA, CAM5.2, CK7, and CK8). In



**Fig. 1.** (A) The central firm area (carcinoma ex pleomorphic adenoma) (arrowhead) is admixed with calcification, and the peripheral surrounding portion (osteoclast-like giant cell tumor) (arrows) is variegated with hemorrhage. (B) The component of pleomorphic adenoma is haphazardly arranged ductal cells in hyalinized stroma. (C) Carcinoma of pleomorphic adenoma is noted in peripheral foci of pleomorphic adenoma. It is composed of cribriform and tubular structures with necrosis and large, hyperchromatic, pleomorphic nuclei with occasional atypical mitoses. (D) Osteoclast-like multinucleated giant cells are evenly distributed amongst numerous atypical mononuclear cells. (E) The border of pleomorphic adenoma (left side) and osteoclast-like giant cell tumors (right side) is sharply delineated by thick fibrous band. (F) p53 expression is in atypical mononuclear stromal cells and not in osteoclast-like giant cells.

the present case, all negative immunohistochemical results of MNCs to epithelial markers (CK7, EMA, CAM5.2, CK5/6, and

CK19) make us hesitate to confirm the epithelial origin. Previously reported positive results for epithelial markers were vari-



**Fig. 2.** Immunohistochemical results on mononuclear stromal cells (MNCs) and osteoclast-like giant cells (OGCs) reveal that MNCs are positive for CD14, CD33, CD45, CD34, CD68, vimentin, fibronectin, and  $\alpha$ 1-antitrypsin (AAT) but negative for CD117, whereas OGCs are positive for CD33, CD68, vimentin, fibronectin, and AAT (arrow) but negative for CD14, CD45, CD34, and CD117 (arrowheads). (A) CD14. (B) CD33. (C) CD45. (D) CD34. (E) CD68. (F) CD117. (G) Vimentin. (H) Fibronectin. (I) AAT.

able and inconstant, and do not provide sufficient evidence for the epithelial origin of MNC.

It has been also debatable whether the origin of OGCs in salivary gland is the same as that of MNCs, as well as whether OGCs are neoplastic or reactive. Tse *et al.*<sup>14</sup> claimed that both of MNCs and OGCs are neoplastic on the basis of the results of loss of heterozygosity (LOH) of the tumor suppressor gene. LOH

foci of MNCs and OGCs were found on Chr17p13, which includes the *TP53* locus.<sup>17</sup> Mutations in *TP53* typically lead to accumulation of the mutated protein, thus allowing the immunohistochemical demonstration of nuclear p53 accumulation to serve as a surrogate for a gene mutation.<sup>18</sup> Although expression of p53 is not always a surrogate for a gene mutation, p53 expression is usually absent in low-grade dysplasia, but is present

in most cases of high grade dysplasia and adenocarcinoma.<sup>18</sup> Our case showed p53 expression in MNCs but not in OGCs. p53 expression in MNCs favors neoplastic rather than reactive nature. It has been demonstrated that osteoclasts can be formed from CD14+/CD45+ monocytes, involving a multistep process during which there is a loss of monocyte markers and a gain of osteoclast markers. Finally, OGCs obtain the CD33+/CD14- phenotype.<sup>3</sup> Therefore, even though MNCs and OGCs are derived from CD14+/CD45+ MOMC, they have different immunohistochemical characteristics.<sup>3</sup> No previous report of salivary OGCT contained an immunohistochemical evaluation for p53 antigen. We first recognized p53 expression in MNCs of salivary OGCT. Shared p53 expression in MNCs and the carcinoma component not necessarily indicates a morphologic transition of MNCs from the accompanied carcinoma considering the negative reaction for epithelial markers of MNCs.

The most challenging differential diagnoses are sarcomatoid carcinoma and giant cell granuloma. The giant cells of sarcomatoid carcinoma are intermingled with carcinoma cells, which are positive for CK.<sup>7</sup> In the present case, the OGCT was sharply delineated from the carcinoma component, and the OGCT was negative for CK. Giant cell granuloma could be found in the carcinoma ex pleomorphic adenoma.<sup>7</sup> But, the size of giant cell granuloma is relatively small (0.5 cm diameter) and the giant cells are scarce and irregularly distributed in the lesion.<sup>7</sup> In the present case, OGCs were numerous and relatively evenly distributed throughout the tumor.

In summary, we report a rare case of salivary OGCT associated with carcinoma ex pleomorphic adenoma. Based on the immunohistochemical staining pattern, salivary OGCT is likely to be related to bone marrow-derived CD14+/CD45+ MOMC.

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