—Case Reports—

Carcinosarcoma ex Pleomorphic Adenoma of the Submandibular Gland in a 64-Year-Old Man: A Case Report

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Carcinosarcoma (CS) is a rare tumor, consisting of both carcinomatous and sarcomatous components. In this paper, we present a case of CS arising from a pleomorphic adenoma (PA) of the submandibular gland. A 64-year-old Japanese man presented with a left submandibular mass that had developed for 20 years with complaints of pain for the last 3 months. Magnetic resonance imaging showed a lesion involving the left submandibular gland. The patient underwent total dissection of the left submandibular gland and left cervical lymph nodes. Upon gross examination, the mass appeared completely covered by fibroadipose tissue measuring 46×42×45 mm; sectioning revealed a solid-white nodule with central bleeding and necrosis, invading into the surrounding adipose tissue. Microscopically, the presence of carcinomatous and sarcomatous components in the fibro-myxomatous stroma was detected, suggestive of pre-existing PA. The carcinoma component was diagnostic of salivary adenocarcinoma, not otherwise specified, whereas the sarcomatous component exhibited features of osteosarcoma characterized by formation of osteoid. As the border between the carcinomatous and sarcomatous components was not evident, CS may have occurred via transformation of the carcinoma into sarcoma. Tumor metastasis was detected in the cervical lymph nodes. Immunohistochemically, AE1/AE3 expression was noted in the carcinomatous component, but not in the osteosarcoma component. Both components were diffusely positive for vimentin. Four months after the operation, the patient developed a metastatic CS lesion in the lung, suggesting tumor aggression. (J Nippon Med Sch 2018; 85: 51–55)

Key words: carcinosarcoma, adenocarcinoma, osteosarcoma, pleomorphic adenoma, salivary gland

Introduction

Carcinosarcoma (CS) is a rare tumor, consisting of both carcinomatous and sarcomatous components. CS can arise in a variety of organs such as the skin, esophagus, lungs, uterus, and pancreas[1–5]. CS can occur in the major salivary glands, such as the parotid (65%), submandibular (22%), and sublingual (13%) glands[6,7]. Salivary gland CS was first described by Kirklin in 1951, and around 70 cases have been reported in the English literature to date[8]. CS accounts for 0.16–1.0% of all salivary gland tumors with a higher incidence of lymphatic and vascular invasion, and subsequent local recurrence[9,10]. So far, the pathogenesis of salivary gland CS remains unclear. One third to one half of salivary gland CS are associated with pleomorphic adenoma (PA), also known as CS ex PA, whereas some cases present as *de novo* salivary gland tumors[11–14]. Herein, we present a case of CS ex PA. We performed histological and immunohistochemical analysis to illustrate the characteristics of the tumor. We further provided insights into the tumorigenesis of CS by reviewing similar cases in the literature.

Case Report

A 64-year-old Japanese man visited a local hospital with

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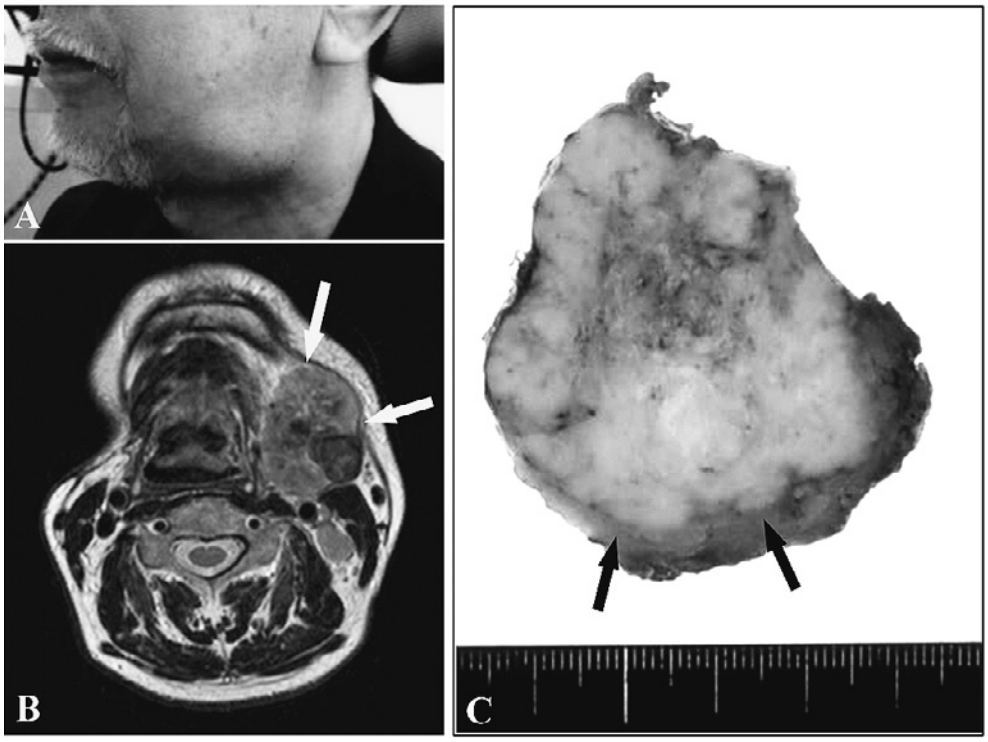

Fig. 1 The patient presented with a bulging mass in his left submandibular gland region (A). Magnetic resonance imaging (T2) revealed an irregularly shaped heterogenous lesion measuring up to 4.5 cm involving the left submandibular gland (B, **arrows**). On gross examination, a solid-white nodule was noted with central bleeding and necrosis, invading into the adjacent adipose tissue (C, **arrows**).

a left submandibular mass that developed over 20 years with complaints of pain over the previous 3 months (**Fig. 1A**). His past medical history was unremarkable. Magnetic resonance imaging showed a heterogenous lesion in his left submandibular gland measuring up to 4.5 cm, highly suspicious of a malignant tumor (**Fig. 1B**). Metastasis to several cervical lymph nodes was also suspected. Thus, fine-needle aspiration biopsy was performed, but the result was not diagnostic. The patient was then referred to our hospital for further examination and treatment. During physical examination, a slightly mobile mass was palpated in the left submandibular region. The patient underwent total dissection of the left submandibular gland and its corresponding cervical lymph nodes.

Upon gross examination, the mass appeared completely covered by fibroadipose tissue, measuring 46×42×45 mm; sectioning revealed a solid-white nodule with central bleeding and necrosis, invading into the surrounding adipose tissue (**Fig. 1C**). Microscopically, proliferation of tumor cells in the fibro-myxomatous stroma was observed, suggestive of pre-existing PA (**Fig. 2A**). Carcinoma and sarcoma components comprised the tumor cells (**Fig. 2B**), and in most areas, a border between these two components was not evident, indicating the transition of these carcinomas into sarcomas. The carcinomatous component was marked by sheets of round-shaped atypical cells with strong connectivity, diagnostic of salivary gland adenocarcinoma, not otherwise specified (NOS), which is a distinct entity under the World Health Organization Classification of Tumours[15] (**Fig. 2C**). The sarcomatous component was characterized by middle- to large-sized polygonal or spindle cells forming an osteoid, suggestive of osteosarcoma (**Fig. 2D**). The carcinomatous and sarcomatous components invaded into the adjacent soft tissue and vascular channels. Further examination revealed tumor metastasis in 4 out of 34 cervical lymph nodes. In the lymph nodes, the metastatic tumor also consisted of both carcinomatous and sarcomatous components. Immunohistochemically, expression of the epithelial cell marker AE1/AE3 was noted in the carcinoma cells but not in the osteosarcoma component (**Fig. 2E**). Vimentin was diffusely positive in both the carcinomatous and sarcomatous components (**Fig. 2F**). No significant expression of other markers such as S-100, calponin, or α-smooth muscle cell actin was detected in the tumor.

Following surgery, the patient received radiation therapy (60 Gy in 30 fractions) and chemotherapy with 14 cy-

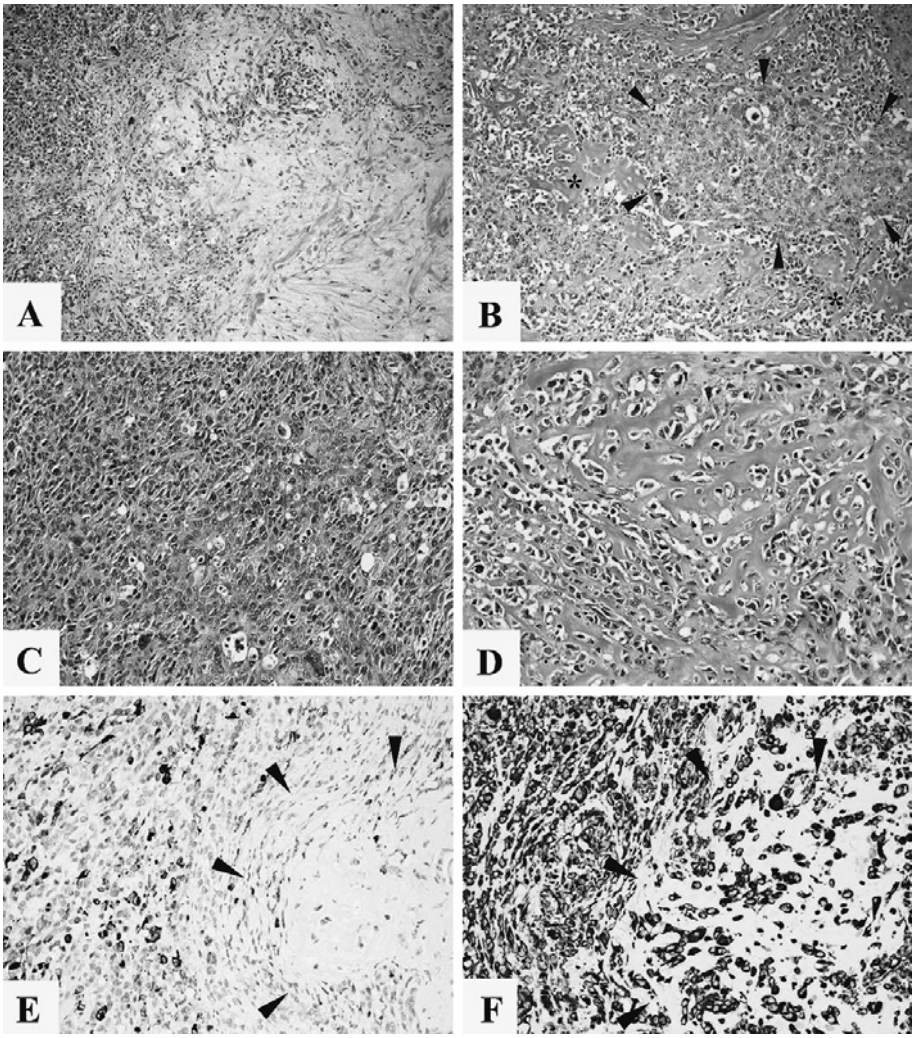

Fig. 2 Histological examination revealed proliferation of atypical cells in the fibro-myxomatous stroma, suggestive of pre-existing pleomorphic adenoma (A). The carcinomatous component (**arrowheads**) is surrounded by the sarcomatous (with osteoid, **asterisks**) components with an indistinct border, indicating the transition from carcinoma into sarcoma (B). The carcinomatous component is characterized by sheets of cohesive cells, compatible with salivary gland adenocarcinoma, not otherwise specified (C). The sarcomatous component exhibits middle- to large-sized polygonal or spindle cells with osteoid formation, suggestive of osteosarcoma (D). Immunohistochemical analysis showed that the carcinoma cells were AE1/AE3 positive, but negative in the sarcoma elements (**arrowheads**) (E). Vimentin was diffusely positive both in the carcinomatous and sarcomatous (**arrowheads**) components (F). Original magnification ×40 (A, B), ×200 (C–F).

cles of TS-1 (a combination of tegafur, gimeracil, and oteracil, 120 mg/day). Four months following the completion of the therapy, however, a computed tomographic examination revealed a lung lesion, depicting a CS metastasis.

Discussion

CS is a rare biphasic malignant tumor consisting of both carcinomatous and sarcomatous components that can affect various organs[1–5]. The most common carcinomatous components are adenocarcinoma, followed by squamous cell carcinoma[16]. The sarcomatous components can show histological features, in decreasing order of frequency, of chondrosarcoma, fibrosarcoma, leiomyosarcoma, osteosarcoma, rhabdomyosarcoma, and liposarcoma[10,14,17–20]. In our patient, histological aspects revealed a combination of adenocarcinoma NOS and osteosarcoma. CS displays a very aggressive behavior due to its high-grade malignant potential. In the salivary gland, patients with CS have a poor prognosis because of a higher incidence of recur-

rence and distant metastasis[21,22]. In our case, the patient initially presented with lymph node metastases, and was given chemotherapy and radiation therapy after surgery. Four months later, he was found to have a metastasized CS lesion in his lung, suggestive of tumor aggression.

The pathogenesis of salivary gland CS is postulated in two main pathways; (1) malignant transformation of pre-existing PA and (2) *de novo* CS with no association to any precursor lesions. In approximately half of the reported cases, CS arises from PA[12]. If there is no evidence of pre-existing benign neoplasm, the tumor should be regarded as *de novo* CS[11]. A distinction of these two can sometimes be difficult when the presence of PA is not histologically evident. Petersson et al. reported that the presence of extensive hyalinized stroma is suggestive of pre-existing PA[18]. In our patient, we identified broad areas of hyalinized stroma, suggesting that CS developed from pre-existing PA. Specific gene alterations have been reported in both PA and carcinoma ex PA. Recent studies have found that pleomorphic adenoma gene 1 (PLAG1) and high-mobility group AT hook 2 (HMGA2) abnormalities are the most common genetic events in both PA and carcinoma ex PA; further investigation of these gene abnormalities would help distinguish carcinoma ex PA from *de novo* carcinoma in the salivary gland[23–25]. Given these reports, we performed immunohistochemical staining for HMGA2, but found no significant positivity in either carcinomatous or sarcomatous components (data not shown). It is possible that cell immunoreactivity may have been compromised by decalcifying solution during the tissue processing. Testing with fresh CS tissues is needed to examine the significance of HMGA2 expression.

Generally, CS can be classified as (1) transformation of carcinoma into sarcoma (so-called CS) and (2) collision of carcinomatous and sarcomatous components (true CS). In other organs, such as the esophagus and duodenum,"so-called CS" is as frequent as "true CS"[19,26]. In the salivary gland, however, whether carcinomatous and sarcomatous phenotypes occur by collision of two independent tumors or they are of clonal origin remains unclear. Vékony et al performed oligonucleotide microarray-based comparative genomic hybridization on the carcinomatous and sarcomatous components of salivary gland CS, and found 75% homology in the DNA copy number profiles between the two components[27]. Based on these results, they concluded that the epithelial and mesenchymal elements in salivary gland CS may have evolved from a single precursor cell. In our patient, we observed some areas in which carcinomas transitioned into sarcomas without distinct borders, suggesting that these two components are of the same origin. Although the exact underlying etiology is still elusive, we assume that it may have occurred via transformation of carcinoma into sarcoma.

In summary, a rare case of CS ex PA in the submandibular gland was described. At the initial presentation, tumor invasion occurred into the adjacent soft tissue with regional lymph node metastasis. Histologically, the carcinoma component was denoted by adenocarcinoma, NOS, whereas the sarcoma component was characterized by osteosarcoma. As the border between the carcinoma and sarcoma components was not distinct, CS was suspected to have developed due to the transformation of carcinoma into sarcoma.

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Conflict of Interest: None.

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