Carcinomatous Change in the Cranial Metastasis from a Metastasizing Mixed Tumor of the Salivary Gland

—Case Report—

Miki FUJIMURA, Takayuki SUGAWARA, Hirobumi SEKI, Yasunari OTAWARA, Tsutomu SAKUMA*, Yoshishige NAKANO**, and Takashi YOSHIMOTO***

Departments of Neurosurgery, *Pathology, and **Surgery, Iwate Prefectural Central Hospital, Morioka; ***Department of Neurosurgery, Tohoku University School of Medicine, Sendai

Abstract

A 57-year-old female who had had a mixed tumor of the submandibular gland for 30 years presented with a cranial metastasis in the ipsilateral occipital region. Detailed histological examinations of the primary tumor failed to detect any carcinomatous component. In contrast, the metastasis contained a carcinomatous component. This histological discrepancy was confirmed by assessment of the expression of Ki-67 antigen in these tumor specimens and comparison with five typical benign mixed tumors. Cranial metastasis of a histologically benign mixed tumor is extremely rare, and a carcinomatous change in the metastatic tumor is apparently unique.

Key words: metastasizing mixed tumor, cranial metastasis, skull tumor, pleomorphic adenoma, Ki-67

Introduction

Mixed tumor is the most frequent type of salivary gland neoplasm. Malignant mixed tumor is much less common and accounts for between 3% and 12% of all cancers of the salivary glands. Malignant mixed tumor has been classified into three histological entities: a) carcinoma ex mixed tumor (carcinoma arising in a mixed tumor), b) carcinosarcoma, and c) metastasizing mixed tumor. Over 90% of malignant mixed tumors are carcinoma ex mixed tumor, which is defined as a mixed tumor in which a second malignant neoplasm develops from the epithelial component. Only the carcinomatous component is known to metastasize. In contrast, the metastasizing mixed tumor is a mixed tumor in which both the primary and metastasizing lesion contain histologically benign mixed tumor.

We describe a 57-year-old female with a cranial metastasis which arose from a mixed tumor of the left submandibular gland. Detailed histological examinations detected no carcinomatous component in the submandibular tumor, whereas the metastasis contained a carcinomatous component.

Case Report

A 57-year-old female presented with a tender subcutaneous tumor which had developed rapidly in the left occipital region since the beginning of July 1995, and was admitted to our hospital on September 19, 1995. She had had a subcutaneous tumor beneath the left angle of the mandible which was compatible with the direct extension of the left submandibular gland for 30 years. She had no previous history of operation or biopsy of the submandibular tumor.

On admission, no neurological abnormality was found. A tender elastic hard mass was identified in the left occipital subcutaneous region. The tumor was round (8 cm in diameter) and relatively well-delineated and immobile. In addition, an elastic hard, non-tender, and mobile mass was palpable in the subcutis beneath the left angle of the mandible. There was no connection between these two tumors.
Detailed examinations of the bilateral mammary glands, subcutis of the entire body, and lymph nodes failed to detect any other tumor. Serum tumor markers including carcinoembryonic antigen, alphafetoprotein, CA15-3, and squamous cell carcinoma-related antigen were within the normal range. Bence-Jones protein and M-protein were negative by electrophoresis.

Radiography disclosed osteolytic change in the left occipital bone. Precontrast computed tomography (CT) revealed a homogeneous and isodense mass in the diploic space. The mass had invaded both intracranial and extracranial structures causing osteolysis. Postcontrast CT showed a heterogeneously enhanced mass (Fig. 1). Axial, sagittal, and coronal magnetic resonance (MR) imaging further defined the structure of the tumor extending into and out of the cranium. Apparently the tumor had also involved the ipsilateral transverse sinus. The occipital lesion was isointense on T₁-weighted images, heterogeneously hyperintense on T₂-weighted images, and heterogeneously enhanced with gadolinium-diethylenetriaminepenta-acetic acid (Fig. 2). Cerebral angiography revealed a hypervascular lesion fed by the ipsilateral middle meningeal artery, occipital artery, and superficial temporal artery (data not shown). The left transverse sinus appeared to be intact. Bone scintigrams with technetium-99m-methylene diphosphonate and tumor scintigrams with gallium showed no high-uptake areas except for the left occipital and submandibular lesions (Fig. 3).

Surgery for the cranial tumor was performed in the right lateral position on October 3, 1995. After skin incision, an elastic hard and well-encapsulated tumor was found under the fascia. The tumor had adhered to the dura mater and invaded the left transverse sinus. The tumor was totally removed piecemeal together with the surrounding bone, invaded dura, and a part of the transverse sinus. The Labbé vein was carefully preserved. The submandibular tumor was totally removed in the Department of Surgery of our hospital on October 24. Her postoperative course was uneventful and the patient became symptom-free. Postoperative MR imaging revealed that the tumor was removed completely (data not shown).

Histological examination of the tumor of the occipital region, which was located mainly in the subcutis, showed invasion into the occipital bone and the cranium. However, the margin of the tumor was relatively well demarcated. The tumor had a papillary, trabecular, and solid alveolar pattern. At several sites, there were conspicuous mucoid changes in the stroma, which resembled cartilage. The tumor cells...
were polygonal and had eosinophilic cytoplasm. Several tumor cells showed squamous cell differentiation. The nuclei were plump. Mitoses were found occasionally (Fig. 4A). Several sites showed a typical mixed tumor with glandular and trabecular patterns (data not shown).

The encapsulated submandibular tumor (4.5 x 2 cm) was a direct extension of the submandibular gland. Histological examination of a section of the entire tumor showed a typical mixed tumor with glandular and trabecular patterns. Tumor cells were closely packed in the dense fibrous stroma, in which hyaline degeneration, partly mucoid degeneration, and ossification were observed (Fig. 4B). A small projection consisting of tumor tissue penetrated the fibrous capsule. However, cellular atypia were minimal (Fig. 4C).

Immunohistochemical expression of Ki-67 antigen was assessed in sections of the occipital and submandibular lesions and compared to specimens of five typical mixed tumors of the salivary glands. Immunostaining was performed by the avidin-biotin complex method, using a SAB-PO (MULTI) kit as specified by the manufacturer (Nichirei, Tokyo). The labeling index was determined visually at 400-fold magnification by counting more than 2000 tumor cells at random. The results were expressed as the percentage of positive cells. The percentage of Ki-67-positive cells was 19.5% for the occipital tumor (Fig. 5A), 0.16% for the submandibular tumor (Fig. 5B), and ranged from 0.12% to 0.31% (mean 0.22%) for the control specimens.

**Discussion**

Detailed histological examinations of the submandibular lesion of our case failed to detect any carcinomatous component. Mitotic activity was absent, but there was an infiltrative growth pattern which had penetrated the capsule of the tumor at several sites. These findings are compatible with those of a histologically benign mixed tumor. In contrast, the cranial lesion of our case contained a carcinomatous component. Immunohistochemical staining using Ki-67 antibody further substantiated the photomicroscopy findings. Ki-67, a nonhistone nuclear
Fig. 4 Photomicrographs showing (A) proliferating tumor cells in the occipital lesion forming solid clumps with many mitotic figures (arrowheads) (×240), (B) cells of the submandibular tumor with a trabecular and glandular structure with mucoid and hyalinized stroma, but no mitoses (×110), and (C) a projection through the fibrous capsule (arrowheads) in the submandibular tumors, but minimal cellular atypia (×50). HE stain.

Fig. 5 Immunohistochemical staining for Ki-67 showing a marked increase in number of positive cells in the occipital lesion (A) in contrast to that of the submandibular tumor (B). Visualization using diaminobenzidine, ×240.

protein, is present only in actively cycling cells and is absent in G0 cells. Therefore, this antibody identifies proliferating tumor cells. The percentage of Ki-67-positive cells in the occipital tumor was much

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higher (19.5%) than that in the submandibular tumor (0.16%), which was almost at the same level as the control specimens (mean 0.22%). These findings indicate that the cranial metastatic lesion was histologically malignant but that the putative primary lesion was relatively benign.

The mechanism of these unusual histological findings may be explained by metastasis of the histological benign mixed tumor to the occipital bone in the usual way, followed by a carcinomatous change only in the metastasis. We believe that the cranial lesion was a metastasis from the mixed tumor of the salivary gland for the following reasons. The histological findings of the cranial lesion were essentially consistent with those of the salivary gland tumor despite the presence of a carcinomatous component. Whole body examination failed to detect any tumor except for the salivary gland and cranial lesion. The histological findings of the salivary gland tumor showed an infiltrative pattern, which suggests metastasizing potential. There was neither macroscopic nor microscopic continuity between the salivary gland tumor and the cranial lesion, but both lesions were relatively close. The long time interval (30 years) from the first presentation to the detection of the metastasis agrees with the known delay of "metastasizing mixed tumor," which ranges from 1.5 to 51 years (averages of 14 to 16.7 years).

"Metastasizing mixed tumor" most frequently gives rise to secondary tumors in the bone and lung. Cranial metastasis is extremely rare. The usual locations of bone lesions are the sacroiliac region, rib, scalp, mandible, femur, humerus, mid to lower spine, and glenoid. Metastatic lesions in bone have a typical osteolytic appearance with some degree of perifocal sclerosis. Our case also had an osteolytic change in the left occipital region shown by both radiography and CT. MR imaging was very useful to clarify the relationship between the tumor and surrounding tissue. Angiography suggested that the ipsilateral transverse sinus was intact, but MR imaging showed that the tumor involved the sinus, which was later confirmed at operation.

The best therapy for malignant mixed tumors is wide local excision of both the primary and metastatic tumors. In our case, surgical excision of both primary and metastatic lesions was successful, and there has been no evidence of tumor recurrence.

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References


Address reprint requests to: M. Fujimura, M.D., Department of Neurosurgery, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-77, Japan.

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