Dedifferentiation occurring in adenoid cystic carcinoma of the tongue

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A 61-year-old man came to the University of Granada School of Dentistry complaining of a mass involving his ventral tongue. Histopathologic examination of the excised specimen showed adenoid cystic carcinoma in which cribriform and tubular patterns were observed, juxtaposed with an undifferentiated carcinoma, large-cell type. No cervical lymph node metastasis was present, and the patient is alive and free of disease 5 years after treatment. To our knowledge, no similar cases have been reported thus far, though other salivary gland malignancies have been described in association with undifferentiated carcinoma, especially in the parotid gland. These neoplasms have been highly aggressive, and the adequacy of the primary surgical resection may be critical in determining the ultimate prognosis and survival.
(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:177-80)

First described in 1853,[1] adenoid cystic carcinoma (ACC) is a malignant glandular epithelial tumor characterized by recurrent growth, late onset of metastases, and poor prognosis. It is the fifth most common epithelial tumor of the salivary glands[2,3] and constitutes approximately 7.5% of such lesions. In the older literature and in some recent studies,[4,5] it was reported as the most common malignant tumor of the intraoral salivary glands, although examples of polymorphous low-grade adenocarcinoma may have been included in these figures inadvertently. The parotid gland, submandibular gland, and palate—in that order—are the sites of most frequent occurrence.[2]

ACC has been described as having tubular, cribriform, and solid patterns, and a combination of all 3 is often found,[6] although the cribriform pattern is most common and is characteristic of the tumor.[7] According to some authors, these pathologic patterns reflect a progression from a greater (tubular) to a lesser (solid) degree of tumor differentiation.[8]

In this report, we describe the case of a man who presented with a mass involving the ventral tongue. The tumor was a composite of ACC and an undifferentiated carcinoma, large-cell type.

CASE REPORT

A 61-year-old man came to the School of Dentistry at the University of Granada in September 1993 for evaluation of a rapidly growing mass, which he had noticed for 1 month. The tumor was located on the ventral tongue, making phonation and deglutition difficult. On review of his medical history, the patient indicated that an adenocarcinoma of his right lung had been excised in 1988 and that there had been no evidence of recurrence or metastasis. His family history was interesting in that a variety of carcinomas involving different sites (lung, mediastinum, and urinary bladder vesica) had affected his father and 2 of his 4 siblings.

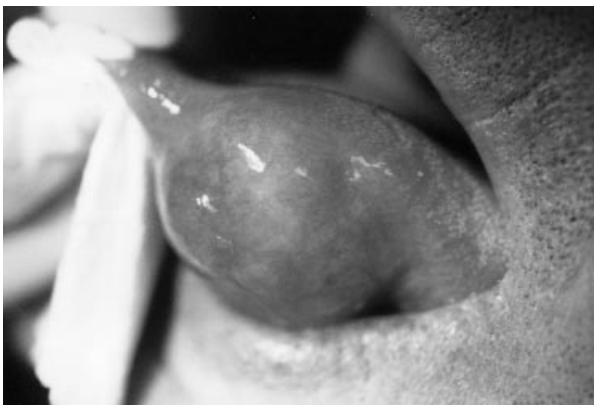

Fig 1. ACC of the tongue.

Intraoral clinical examination showed a round mass, 3 cm in diameter, located on the left ventral tongue and covered by nonulcerated mucosa (Fig 1). Tongue mobility was not affected, and no enlarged cervical lymph nodes were found. The lesion was removed surgically. Some areas of necrosis and hemorrhage were observed macroscopically on its cut surface.

Histopathologic examination of the tissue showed the presence of a classic ACC with a predominant cribriform pattern (Fig 2) and areas with a tubular pattern. Some tumor lobules with a classic cribriform pattern were seen in close proximity to areas of anaplastic carcinoma characterized by large pleomorphic nuclei and high mitotic activity. This second component of the tumor, an undifferentiated carcinoma of large-cell type (Fig 3), was in some areas separated by fibrous septa from the classic ACC (Fig 4, *A*); in others areas, however,

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Received for publication Oct 2, 1998; returned for revision Dec 14, 1998; accepted for publication Mar 23, 1999.

1079-2104/99/$8.00 + 0 **7/14/99046**

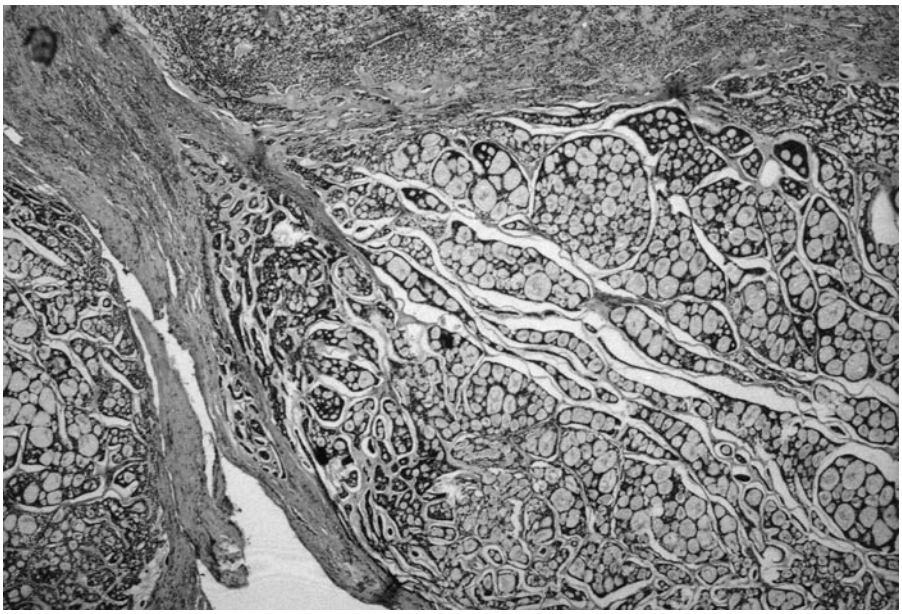

Fig 2. Typical ACC portion of tumor with cribriform pattern.

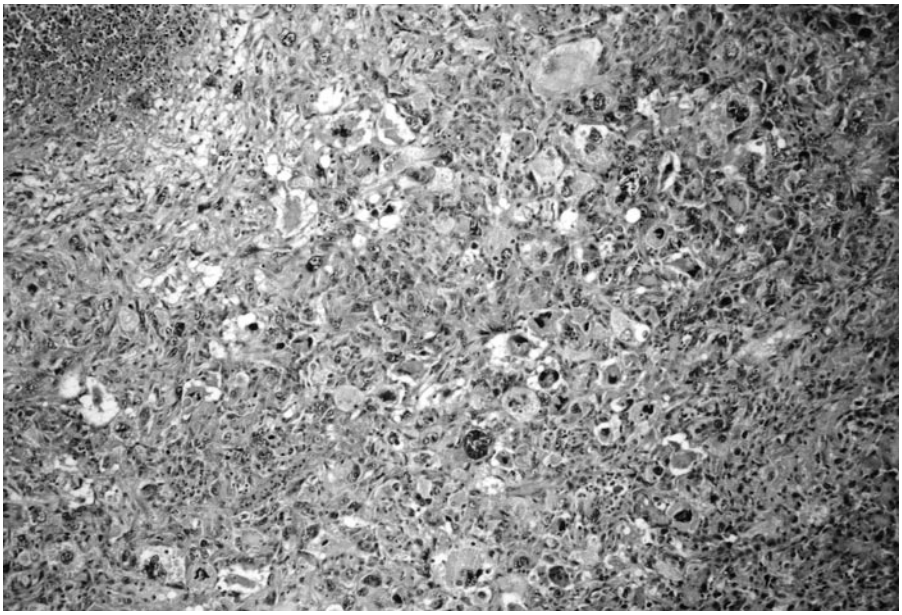

Fig 3. Undifferentiated carcinoma area of tumor. There are bizarre multinucleated giant cells and high mitotic activity.

there was an intermingling of the 2 neoplastic cell populations (Fig 4, *B*). The relative proportion of the 2 components was roughly 1:1.

No intravascular invasion was noted. A small tumor island of the ACC was seen in the proximity of a peripheral nerve. The tumor had a well-defined periphery in some areas, but infiltrative margins were seen in others. Abundant hyalinized stroma was evident focally.

A comparison of the tongue lesion and the pulmonary adenocarcinoma removed in 1988 was made; the 2 neoplasms did not appear similar, which tended to rule out a metastatic deposit in the tongue. The final diagnosis was ACC in combination with an undifferentiated carcinoma. A partial glossectomy and modified radical lymph node dissection were performed. Histopathologically, no residual tumor was seen in the tongue, and none of the cervical lymph nodes were involved by the

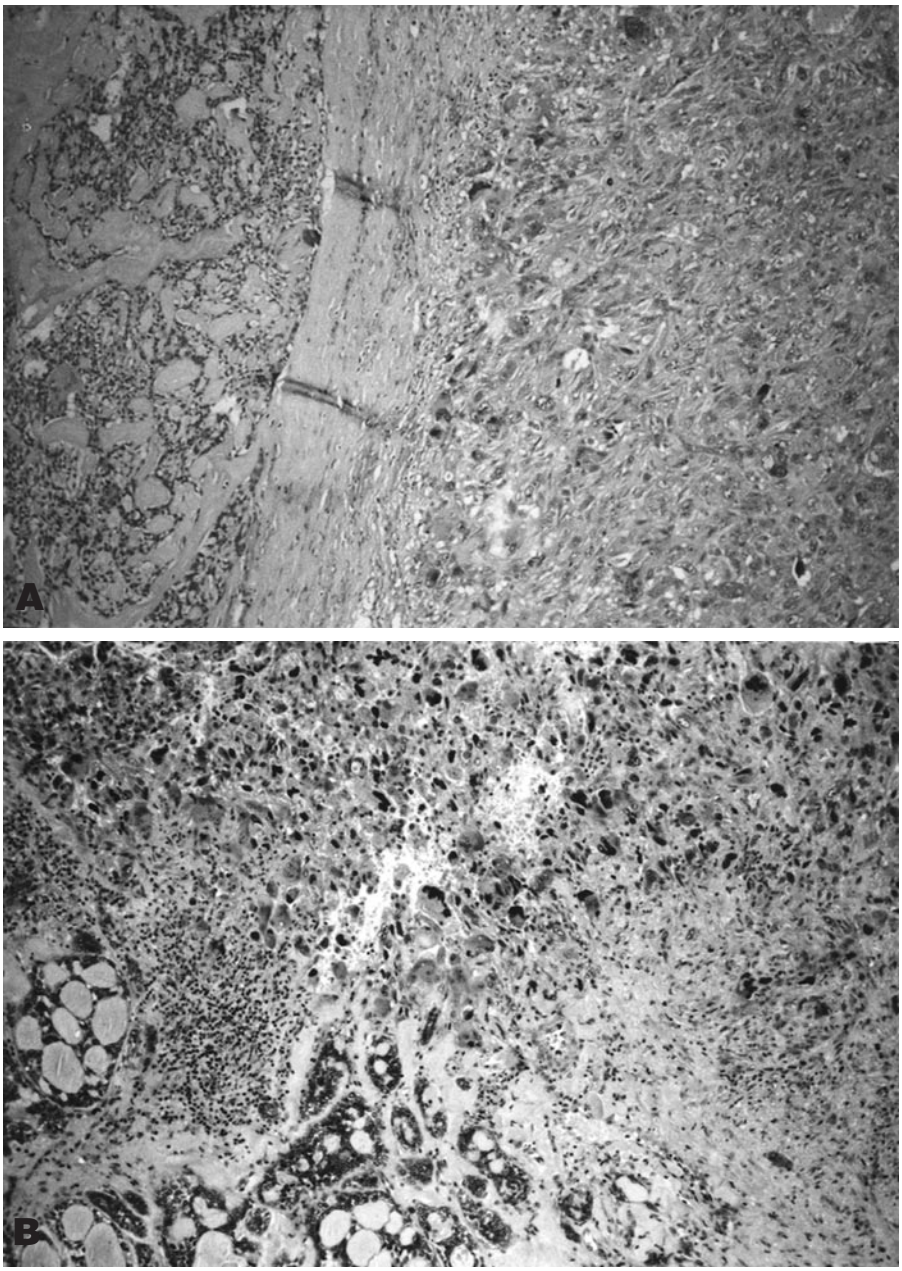

Fig 4. **A,** fibrous septa separate 2 components of tumor. **B,** undifferentiated cells seem to infiltrate classic areas of ACC.

neoplasm. At the present time, after 5 years of follow-up, the patient is alive and shows no sign of recurrent disease.

DISCUSSION

Since the first description of ACC in 1853, the perceived prevalence of this tumor has changed with the recognition of several newly described types of salivary gland carcinoma. The Armed Forces Institute of Pathology[2] has identified twice as many polymorphous low-grade adenocarcinomas (tumors frequently misinterpreted as ACC) as ACCs in the minor salivary glands. In the files of the Armed Forces Institute of Pathology, ACC was found to be the fifth most common malignant epithelial tumor of salivary gland origin, after mucoepidermoid carcinoma, not otherwise specified adenocarcinoma, acinic cell adenocarcinoma, and polymorphous low-grade adenocarcinoma.

The present case of ACC showed a mixture of cribriform and tubular patterns, and areas of anaplastic carci-

noma were observed in proximity to the cribriform nests. Areas of "dedifferentiated" or undifferentiated carcinoma have been described as a component of some acinic cell adenocarcinomas.[9-13] In the case of carcinoma ex-pleomorphic adenoma, the carcinomatous element is most often undifferentiated carcinoma or adenocarcinoma.[2] To our knowledge, no ACC associated with undifferentiated carcinoma has been reported in the literature thus far. There was a recent case of hybrid carcinoma of salivary gland composed of an ACC and a poorly differentiated adenocarcinoma.[14]

For the hybrid carcinoma, the differential diagnosis should include collision tumor, biphasically differentiated tumor, and synchronous and multiple recurrences of salivary gland tumors. In the present case, the ACC was associated with an undifferentiated carcinoma, large-cell type. Undifferentiated carcinomas are uncommon neoplasms of the salivary glands but are histologically similar to undifferentiated carcinomas that arise in other organs; therefore, metastatic carcinoma must be included in the differential diagnosis.[2]

Once the possibility of a metastasis of the pulmonary adenocarcinoma had been ruled out, several explanations for this process were possible: (1) a single pluripotential cell could have evolved into different cell forms in the same tumor[8]; (2) the tumor might be due to a collision between 2 different tumors appearing by chance in the same area; (3) the anaplastic areas of the tumor might have resulted from "dedifferentiation" in the neoplasm. Perhaps the pathogenesis of dedifferentiation parallels that of dedifferentiated sarcomas—liposarcomas,[15] osteosarcomas,[16] and chondrosarcomas[17]—in which a low-grade tumor presumably undergoes transition to high-grade malignancy. Regardless, the molecular events underlying "dedifferentiation" are unknown.[13]

In the present case, the relative proportion of undifferentiated carcinoma and typical ACC was roughly 1:1, with fibrous septa separating the 2 components in some areas and undifferentiated carcinoma infiltrating typical ACC in other areas. The published reports of cases of dedifferentiated acinic cell carcinoma have noted that in a given tumor either element may predominate and the interface between the 2 components may vary.[11,13]

Regarding the clinical features of salivary gland tumors with undifferentiated areas, the presence of facial nerve involvement, pain and/or tenderness, and the development of metastatic disease are common. In general, these are lethal neoplasms.[10,11,13] Treatment of such tumors must be dictated by the undifferentiated carcinoma component, and radical resection with elective neck dissection should be performed. Currently, our patient is alive and shows no evidence of disease after 64 months of follow-up.

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