Carcinoma ex-pleomorphic adenoma of upper lip showing copy number loss of tumor suppressor genes

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Background. Carcinoma ex-pleomorphic adenoma (CXPA) is a malignant salivary gland tumor that arises rarely in the minor salivary glands. Although the etiology of CXPA remains unclear, the role of some tumor suppressor genes and oncogenes in CXPA is documented; however, other genes still need to be studied.

Study design and objective. An uncommon case of CXPA involving the upper lip is presented, which was analyzed by a panel of tumor suppressor genes by multiplex ligation-dependent probe amplification.

Results. The genes investigated in this study, a loss of copy number was detected for *CASP8*, *CD44*, *CDH1*, *DAPK1*, *ESR1*, *RASSF1*, and *TP73*. Immunohistochemical reactions for the validation of some of these results showed negativity for *CD44*, *RASSF1*, and *p73*.

Conclusion. A loss of copy number of the genes *CD44*, *RASSF1*, and *TP73* may contribute to the carcinogenesis of CXPAs.
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Carcinoma ex-pleomorphic adenoma (CXPA) is a rare malignant tumor that affects the salivary glands and corresponds to 3.6% of all salivary gland neoplasms and 11.7% of all salivary malignancies.[1,2] CXPA occurs more commonly in the parotid and submandibular glands but is extremely rare in minor salivary glands.[3] The main site of occurrence of CXPA in the minor salivary glands is the palate, but involvement of other locations such as the buccal mucosa, floor of the mouth, alveolar ridge, gingiva, retromolar area, nasopharynx, and upper and lower lips has been described.[4-12]

The pathogenesis behind the malignant transformation of pleomorphic adenoma (PA) process remains unclear, and alterations of tumor suppressor genes and oncogenes may be relevant to the tumorigenesis process. A limited group of genes and markers of PA malignant progression have been described in previous studies.[13-15] Therefore, the objective of this study was to determine copy number loss in a panel of tumor suppressor genes using multiplex ligation-dependent probe amplification (MLPA) in a case of CXPA involving the upper lip. Immunohistochemical analysis was performed for the validation of MLPA results as described in the literature.[16-18]

PATIENT AND METHODS

A 69-year-old man was referred for the evaluation of a nodule on his right upper lip of 4 years duration. Upon clinical examination, a semifixed fibroelastic nodular painless lesion on the right side of the upper lip was observed, measuring approximately 2 × 2 cm (Figure 1). With pleomorphic and canalicular adenoma as the main clinical diagnoses, the lesion was surgically removed.

Microscopic examination of the surgical specimen showed an uncapsulated well-circumscribed lesion, showing intense hyalinization with clusters and nests of epithelial cells and ductal structures composed of epithelial and myoepithelial cells (Figure 2*A*). In some areas, the epithelial cells were cuboidal, with eosinophilic cytoplasm and normal nuclei, whereas the abluminal myoepithelial cells were spindle-shaped with more hyperchromatic nuclei. There was no evident pleomorphism, cellular atypia, or mitoses (Figure 2*B*). These microscopic aspects were suggestive of PA.

Nevertheless, the ducts were larger in other regions and were formed by pleomorphic cells with increased

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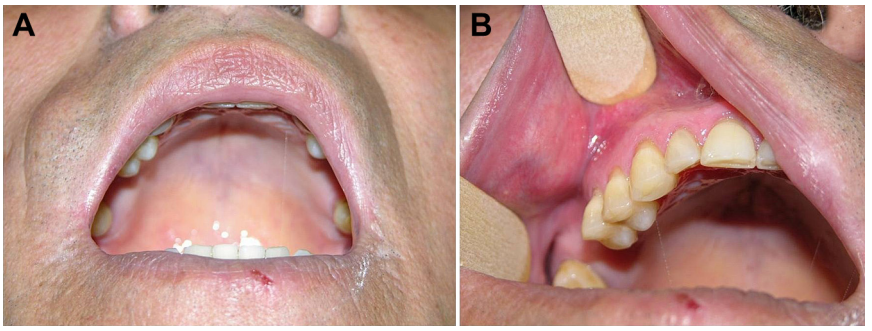

Fig. 1. **A** and **B,** Clinical aspects of CXPA involving the upper lip (right side).

nucleus/cytoplasm ratios, hyperchromatic nuclei, and prominent nucleoli (Figure 2*C-E*). These areas showed a high immunoexpression of Ki-67 (68.7%) (Figure 2*F*), whereas the PA area showed a low proliferative index (4.8%). The final diagnosis was of minimally invasive CXPA, with a malignant component classified as adenocarcinoma not otherwise specified (NOS).

Clinical and radiographic (chest X-ray) investigations to detect metastases were negative. Surgical margins were not satisfactory because the tumor cells were extending close to the surgical margins, but the patient declined complementary surgical treatment. After a follow-up period of 30 months, there was no evidence of recurrence or metastases.

Tumor DNA was extracted from paraffin-embedded tissue samples using Qiagen extraction kits (Qiagen GmbH, Hilden, Germany) in accordance with the manufacturer's recommendations. The carcinomatous and benign areas were extracted using a punch with a 3 mm diameter, but a good concentration and quality of DNA was obtained only from the malignant area. To improve the quality of the isolated DNA, an elaborate extraction protocol specific for paraffin-embedded tissues was applied, which included thorough deparaffinization with xylene, methanol washes to remove all traces of the xylene, and a 24-h incubation period in 1 mol/L sodium thiocyanate to reduce cross-linking. Subsequently, the tissue pellet was dried and digested for

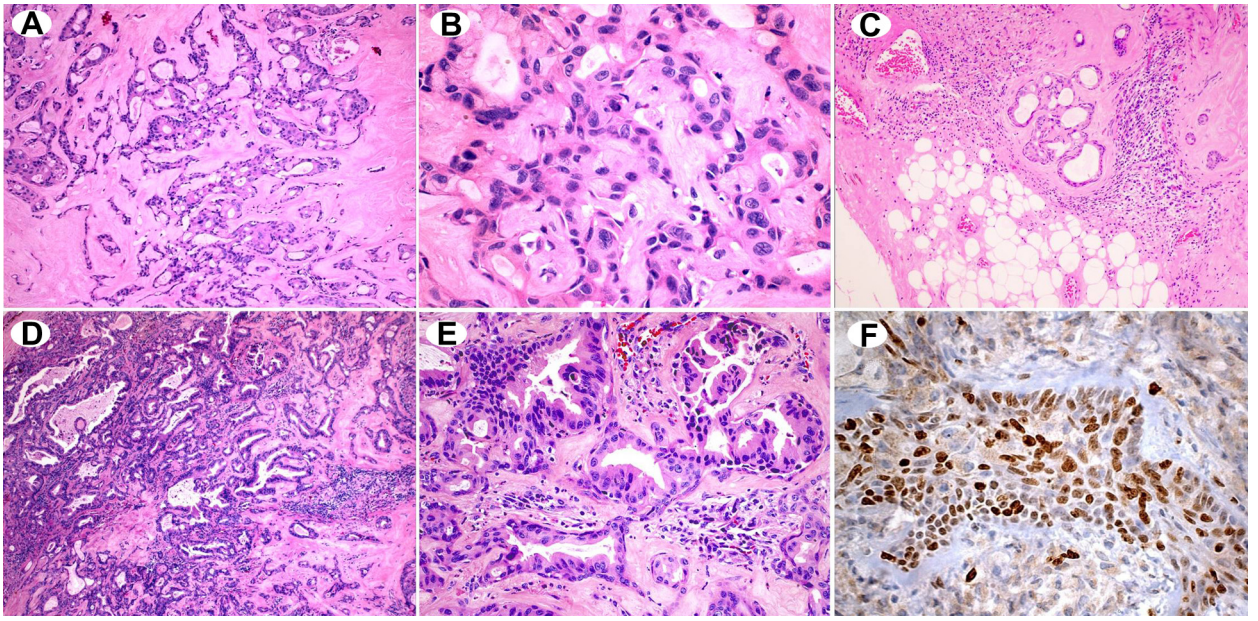

Fig. 2. Carcinoma ex-pleomorphic adenoma of the upper lip. **A,** Area of PA showing intense hyalinization, with clusters and nests of epithelial cells forming typical ductal structures of PA (hematoxylin and eosin [H&E], original magnification ×100). **B,** Epithelial cells forming ducts and presenting mild nuclear pleomorphism (H&E, original magnification ×400). **C,** Area of minimal invasion showing malignant cells in the adipose tissue surrounding the lesion (H&E, original magnification ×100). **D** and **E,** Areas of malignant transformation showing large and irregular ducts formed by hyperchromatic pleomorphic cells (H&E, original magnification ×100 and ×400). **F,** High nuclear immunoexpression of Ki-67 in the malignant cells forming a solid island (H&E, original magnification ×400).

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