B-ENT, 2007, **3**, 27-29

Carcinoma ex pleomorphic adenoma of the submandibular gland with distant metastases

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Key-words. Adenocarcinoma; ex pleomorphic adenoma; submandibular gland

Abstract. *Carcinoma ex pleomorphic adenoma of the submandibular gland with distant metastases.* A case of metastatic carcinoma ex pleomorphic adenoma (PA) of the submandibular gland is reported. While reports of local recurrence of this cancer are numerous, few cases of distant metastases have been reported. We report a case of a 52-year-old male patient with a history of PA diagnosed ten years previous. The patient presented reporting that the mass had increased size and pain during the previous six months. Needle biopsy results of this mass were compatible with a poorly differentiated carcinoma of the salivary ducts. Radical surgery with wide right neck dissection was performed with curative intent. Three years post-surgery liver and bony metastases were detected. In conclusion, the potential for malignant transformation of PA demands close follow-up of younger patients.

Introduction

The salivary glands are common sites for a variety of tumours; the parotid glands are the most common site followed by the submandibular glands. Pleomorphic adenoma (PA) is a benign epithelial tumour of adenoid structure preferentially arising from the parotid gland. PA represents 60-70% of all tumours involving the major salivary glands; the submandibular gland is involved in about 8% of cases.[1] Recurrent PA usually occurs in the distribution of the primary lesion. There are numerous reports of local recurrence and a few reported cases of distant metastases. Extensive seeding throughout the entire ipsilateral neck is rare. Treatment involves a combination of radical surgery, radiotherapy, and chemotherapy.

These slow-growing benign tumours can undergo malignant transformation, although it is uncommon, occurring in 2% to 23% of cases. In a noteworthy number of patients, a phenotype with distinct properties of malignancy develops inside the benign tumour.[2] This transformation potential increases according to the time of evolution of the tumour. Patients with malignant transformation have died from disseminated lung and bone metastasis.[3]

Case report

We present the case of a 52-year-old male ex-smoker with an antecedent right neck mass, and a history of submandibular gland PA diagnosed by fine needle aspiration technique. The patient refused surgery at the time of diagnosis. Ten years later the patient presented, reporting a progressive increase in the size and pain of this mass over the preceding 6 months. CT scan (Figure 1) revealed a right neck mass with invasion into the floor of the mouth and infiltrates into the sternocleidomastoid muscle and internal jugular vein. Lymph node metastases were observed in the left side of the neck. Results of the needle biopsy were compatible with a poorly differentiated carcinoma of the salivary ducts.

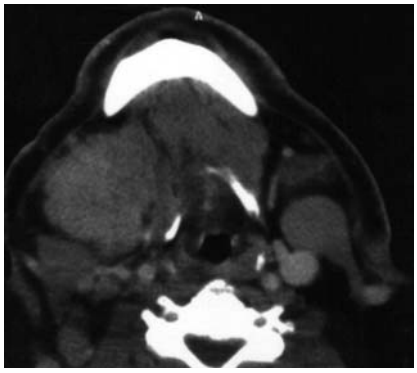

Figure 1
Neck CT scan shows a mass in left submandibular gland.

Radical surgery with wide right neck dissection was performed. The submandibular glands were excised including the right digastric, mylohyoid and masseter muscles. Pathology findings indicated an

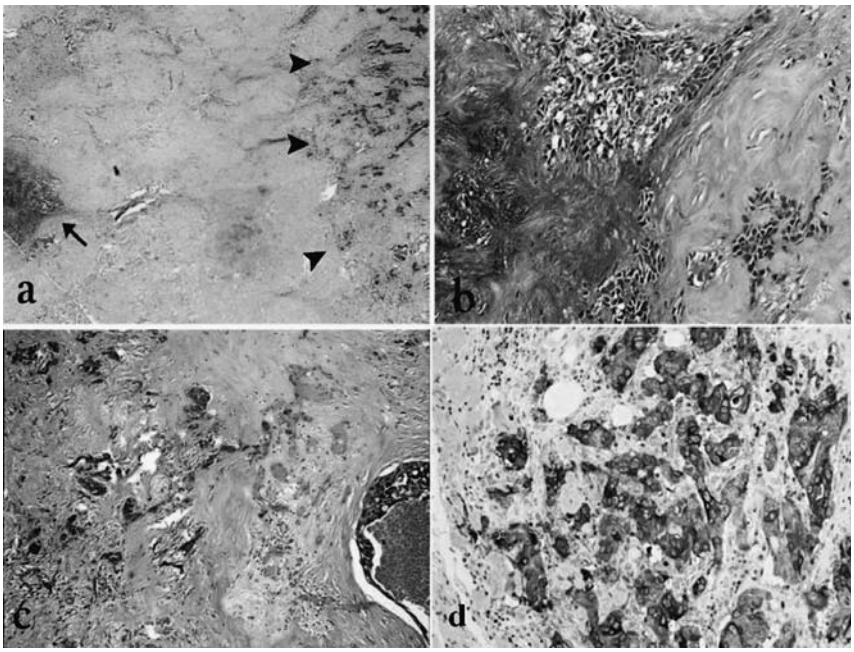

Figure 2
a: Infiltrative adenocarcinoma (arrows) arising in a PA (arrows), hematosin & eosin stain × 100; b: detail of PA, hematosin & eosin stain × 100; c: infiltrative adenocarcinoma detail × 100 in hematosin & eosin stain; d: adenocarcinoma cells stained positive for carcinoembryonic antigen (CEA) × 100.

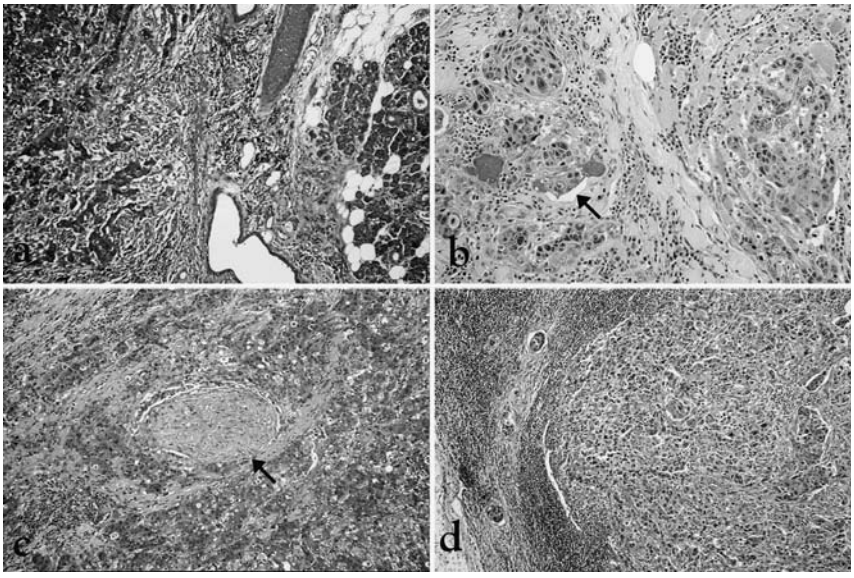

Figure 3
Infiltrative adenocarcinoma of submandibular glands in hematosin & eosin stain × 160; a: normal submandibular gland; b: vessels infiltration (arrow); c: neural weaves (arrow); d: lymph node.

infiltrative adenocarcinoma arising from a PA with extensive invasion to nerves, vessels, muscles, and lymph nodes (Figures 2,3).

Three years post-surgery liver and bony metastases were identified (Figure 4), and chemotherapy and cobaltotherapy were initiated. The patient died four years after surgery without local recurrence.

Discussion

Complete surgical removal of the PA is the treatment of choice; radiotherapy and chemotherapy are not standard. However, in cases of large, locally diffuse, and infiltrating PAs with high malignant potential, resection should be followed by radiotherapy. Debates concerning the benefit of chemotherapy persist. In this case radiotherapy was not performed because no local recurrence was observed; however, the standard of care for these tumours is resection and radiotherapy. In cases of PA of the parotid gland, total parotidectomy or subtotal petrosectomy with facial nerve resection in selected cases may reduce the risk of multiple episodes of PA recurrence.[3]

Truly benign PAs do not need radiotherapy. In carefully selected patients local excision of recurrent disease is sufficient for controlling disease progression.[4] Failure to perform careful surveillance and treatment can allow the primary tumour to progress toward a more malignant phenotype, and deny the patient a high expectation for a complete cure.[5] Incomplete excision of a PA exposes the patients to a high risk of recurrence and tumour spread, making secondary surgery more difficult or a malignant transformation with a poor prognosis more likely. Carcinoma arising in a PA is frequently aggressive, and 40% to 50% recur.[6]

The degree of malignancy of the tumour is fundamental to the prognosis and the survival of the patient. In the case of the submandibular gland, these tumours

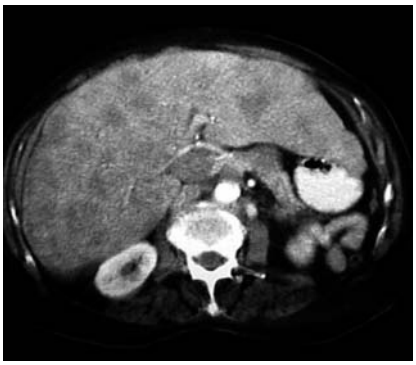

Figure 4
Abdominal CT showing liver metastases

tend to invade the normal gland and perineural weaves. Presently there are no generally accepted histopathological parameters for differentiating the "common" PA from the metastatic PA.[7] Interestingly, Cyclooxygenase-2 (Cox-2) levels are elevated in metastatic PAs, suggesting that Cox-2 may play a fundamental role in the malignant transformation of benign Pas.[8] As well, overexpression of the genes HMGIC and MDM2 seems to increase the possibility of malignant transformation in the PA.[9] In biomarker analysis, P53 and c-ErbB-2 proteins appear to be involved at an early stage of malignant progression of PA.[10]

PA of the submandibular gland is rare and can be difficult to diagnose. Despite the clinical suspicion of malignancy, in some cases detecting carcinoma ex PA cannot be achieved by examination of a preoperative biopsy or a frozen section removed intraoperatively, as the lesion may only show mild cytological atypia with no frank malignant features. Only a thorough evaluation of the resected tumour enables the diagnosis of the malignancy.[11] Heterogeneous histology, high suspicion of malignant transformation, and incomplete capsules that favour recurrence are the most significant characteristics of a PA. In other case reports, histopathological examination revealed that adenocarcinoma cells with hyperchromatic nuclei and mitotic figures proliferated in PA.[12,13]

Conclusion

In conclusion, metastatic PA is likely to be unrecognized and therefore PA must be considered a low-grade, potentially lethal malignant disease when it presents. Evidence of malignant disease may only be present in submicroscopic features and genetic alterations. Furthermore, the potential for malignant transformation demands close follow-up and early intervention, particularly for younger patients.

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