HISTOPATHOLOGIC AND IMMUNOHISTOCHEMICAL STUDY IN ONE CASE OF CYSTADENOMA OF PAROTID GLAND BECOMING MALIGNANT

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Summary. Cystadenoma and cystadenocarcinoma of the salivary glands are rare tumors, approximately half of cases being diagnosed at the level of parotid. The studied tumor associated both benign and malign zones, with deep infiltrating character in the adjacent structures. In both areas the growing pattern was predominantly cystic and papillary, and the proliferated neoplastic cells were majority cubical or columnar, with low grade of nuclear pleomorphism in the becoming malign areas, discordant with the infiltrative character of the neoplasm. Immunohistochemically, we investigated the tumor with AE1-AE3, CEA, SMA, S-100 and PCNA.

Key words: papillary cystadenoma and cystadenocarcinoma, histopathology, immunohistochemistry.

INTRODUCTION

Salivary glands cystadenoma is a rare benign tumor. The incidence of this neoplasm is underestimated in specialty literature, being often interpreted as a hyperplasic process of the salivary ducts. It represents 4% of the benign epithelial tumors with this localization, developing both in the major salivary glands, with predilection in parotid, and the minor salivary glands, especially the one from the level of lip and oral mucosa. The diagnostic is made in all the decades of life, but more frequent at persons from the VI–VIII decade of life, and more frequent to he females [1].

The malign correspondent of the cystadenoma of the salivary glands is cystadenocarcinoma, which, in over half of cases, are localized in the minor salivary glands, the rest being diagnosed in parotid. It occurs especially at patients over 60 years old, with equal incidence on sexes.

Tumor is included in the group of low-grade malign epithelial tumors, having a lent growing, only in rare cases affecting the facial nerve and infiltrating the adjacent bone structures. The recidivate rates, such as the regional lymphatic metastases are considered fewer than 10% [1–4]. The origin of the salivary glands tumors is still controversial.

It is considered that at the origin of the diversity of this type of tumor would be the unique stem cell (reserve cell) from the intercalated units of ducts, with capacity of differentiation predominantly to the luminal cells line, the abluminal cells line or both cellular lines. According to this theory, the salivary cystadenoma and its malign variant belong to the group of predominant luminal differentiated tumors [5].

Actually, a theory sustains the existence of one undifferentiated, pluripotent cell at the level of the intercalary and striated channels, probably implicated in the regeneration of the salivary parenchyma and in genesis of salivary metaplastic or neoplastic changes [6].

MATERIAL AND METHOD

The surgical pieces came from a male patient from the OMF Clinic diagnosed with tumor of the parotid. The piece was processed by usual techniques by inclusion in paraffin, followed by staining with haematoxylin-eosine. In parallel, the fragment was processed by immunohistochemical methods LSAB 2; we took in consideration the expression of tumor for AE1-AE3, CEA, vimentin, SMA, S-100 and PCNA.

RESULTS

The 62 years old male patient was clinically diagnosed with tumor of parotid. Grossly, the surgical piece was partially fibrous encapsulated, gray, with diameter of 1.5 cm. On section, we noted the presence of numerous microcystic spaces separated by fibrous septa, filled with mucous content and small solid zones. Microscopically, on serial sections, the tumor was partially delimitated by a dense, fibrous capsule.

Its structure was multiloculated on large areas, containing numerous cysts with varied dimensions separated by fibrous septa. The cystic lumens were filled with eosinophilic, amorphous material and rare inflammatory cells, or small groups of desquamated epithelial cells. The cystic walls were almost entirely lined by cubic or columnar epithelia with benign aspect, which rarely formed papillary projections centered by a connective-vascular axis. Occasionally, areas of oncocytic and mucinous metaplasia were present. Mitosis was rare and typical (Figure 1).

Together with these aspects, were large areas with anastomosing cystic spaces and frequent papillary structures, sometimes with complex architecture and small solid areas (Figure 2).

Both patterns had an infiltrative development, sometimes exceeding the glandular parenchyma and infiltrated the adjacent bone (Figure 3).

Frequent, in the interior of the cysts existed detached islands of neoplastic cells in a homogeneous eosinophilic mass. Cystic and papillary structures were lined by cubic or columnar, frequent stratified epithelia, alternating with small areas with mucinous, clear, or squamous cells (Figure 4).

The nuclei of the neoplastic cells had a reduced grade of pleomorphism, evident nucleoli and rare mitosis. In the tumoral stroma reduced inflammatory infiltrates, predominantly lymphocytes were present. Nuclei of the neoplastic cells had a low-grade polymorphism, evident nucleoli and rare mitosis. In the tumoral stroma were present only small inflammatory infiltrates, predominantly lymphocytes.

The immunohistochemical study revealed isolate and slight positivity for AE1-AE3, both in the benign and malign areas of tumor, with a more intense staining in the squamous metaplasia areas (Figure 5).

Immunostaining for CEA was diffuse intense positive at the level of the proliferated cells, especially on the luminal versant; immune reaction made for vimentin and SMA was negative (Figure 6). S-100 positivity was slight and only zonal (Figure 7). PCNA was higher than 15% in malign tumoral areas and under 7% in benign tumoral areas (Figure 8).

DISCUSSIONS

Salivary glands cystadenoma and cystadenocarcinoma are rarely mentioned in literature, both because they low incidence and the sub estimation of this diagnosis. Cystadenoma is frequent interpreted as a hyperplastic lesion of the salivary ducts and cystadenocarcinoma is considered like a low-grade polymorphous adenocarcinoma, a muco-epidermoid or acinic cells or salivary ducts carcinoma [1, 7].

Tumor studied by us presented both benign and malign proliferation- this fact constituting an argument pro the classification of the benign variant of the tumor in the tumoral group of lesions. The predominant pattern of proliferation was cystic and papillary, solid areas being present only sporadic, in areas with infiltrative development. Both in benign and malign areas, papillary structures were present, yet in the cystadenocarcinoma areas the papillae had a more complex architecture, sometimes with anastomosing.

The lining epithelia of cysts and papillae were dominantly cubic or columnar, with homomorphous aspect in benign areas and low-grade nuclear polymorphism in the malign areas, uncorrelated with the infiltrative evolution of tumor. They were small areas with oncocitic, mucinous, clear or squamous tumoral cells, both in benign and malign areas.

In the fibrous septa discrete inflammatory infiltrates were present. In literature, the majority of reported cystadenocarcinoma are low-grade tumors

associated only with infiltrative growing in the vicinity and, only sporadic, with lymph nodes metastases [3, 4, 8].

The immunohistochemistry confirmed the epithelial ductal origin of neoplasm (CEA, AE1-AE3, vimentin, SMA) and permitted us to appreciate the degree of cellular proliferation.

Normal salivary glands are CEA positive at the level of serous acinar cells (with peri-cytoplasmic pattern), the luminal membrane versant, columnar luminal cells of the intercalary ducts (on the luminal versant) and in the intraluminal secretion product [9–11]. In carcinoma of the salivary glands, CEA immunostaining is present with variable sensibility and specificity depending on the histopathological variant.

The studied tumor was CEA diffuse and intense positive in the proliferated epithelial cells, especially on the luminal versant.

The monoclonal antibody anti cytokeratin AE1-AE3 is a cocktail of two monoclonal antibody AE1 (CK 10, 13, 14, 15, 16 and 19) and AE3 (CK 1, 2, 3, 4, 5, 7, 8) used for detection of some types of cytokeratins present both in the normal human epithelial tissues and in them neoplastic equivalents [12]. It reacts with epidermis, squamous stratified epithelia of the internal organs and with simple epithelia, immunostaining being uniform distributed in entire cytoplasm.

For the salivary glands the CK8, 18 and 19 positivity is constant in the ductal cells, which occasionally are CK 14 positive, especially the basal one, but it is missing in the myoepithelial cells that are constantly CK14 positive. In contrast, the serous and mucous acinar cells express only CK 8 and 18. Immunoreactivity to CK19 was constantly noted in the ductal luminal cells and inconstant in basal ductal cells and very rare in acinic cells [13].

For the investigated tumor, AE1-AE3 reaction was reduced as intensity and only with focal character, especially in the areas of squamous metaplasia.

S-100 immunoreaction of the normal structures of the salivary glands indicates the presence of reactivity from the ductal epithelial cells and periacinar and periductal myoepithelial cells and at the stromal level from the histiocytes, Schwann cells and satellite cells [14].

In our case, the positivity for S-100 was with zonal character and with low intensity, only in the epithelial structures of the tumoral parenchyma.

In the normal salivary glands, the epithelial cells, including the myoepithelial cells, are vimentin negative, positivity being limited to interstitial fibroblasts, endothelial cells, smooth muscular fibers and he pericytes from the glandular vascular system (Grandi *et al.*, 2000; Morinaga *et al.*, 1987; Ogawa *et al.*, 2003). The tumoral parenchyma of the investigated tumor was negative to vimentin.

SMA is a specific marker for the myoepithelial proliferation. In our case, the tumor was SMA negative in the tumoral parenchyma and positive at the level of the vascular component of stroma. Being intense and diffuse positive for CEA, focal positive for AE1-AE3 and with reduced and focal intensity for S-100,

together with the absence of staining for vimentin and SMA, the epithelial ductal origin of the studied tumor was confirmed.

The degree of cellular proliferation was investigated with PCNA, both in the benign and in the malign component of tumor. PCNA index was over 15% in malign areas and only under 7% in benign areas. The low values of the PCNA index in malign areas are in correlation with the low grade of nuclear polymorphism, but are discordant with the deep infiltrative character of tumor.

CONCLUSIONS

We consider useful the presentation of this case of papillary cystadenocarcinoma of parotid, both by the low incidence at this site and the problems of diagnosis: the benign histopathological aspect with areas of epithelial hyperplasia with minim malign characteristics, but the bone's invasion confirmed the malign character.

Tumor associated evident areas of benignity and areas of malignisation, with invasive growing until the adjacent osseous structures. On the whole, both areas presented cystic and papillary pattern, neoplastic cells having cubic and columnar morphologic aspect. Nuclear polymorphism was reduced, even in malign areas, discordant with the infiltrative character of the tumor.

Immunohistochemical investigation confirmed the epithelial nature, probably ductal, of the neoplasm, by the intense positivity to CEA, low positivity for cytokeratin and S-100, and negativity for vimentin and SMA.

Using PCNA index, we investigated the intensity of the cellular proliferation. The values, even they were bigger in malign areas, comparative with benign one, and correlated with the reduced polymorphism, were in discordance with the profound infiltrative character of the tumor.

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Received: 14 April, 2004

Accepted: 10 October, 2004

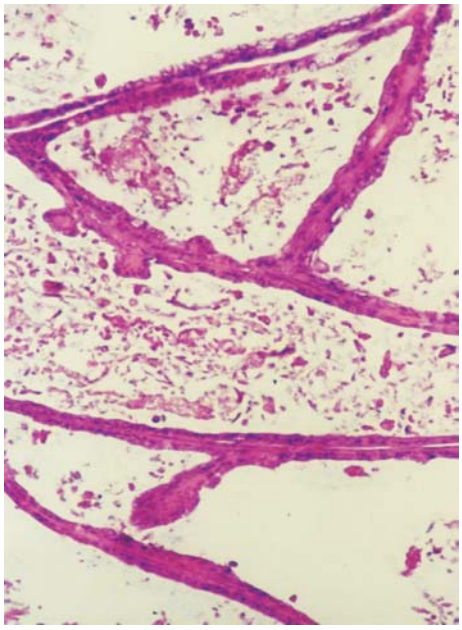

Figure 1 – Cystadenoma of parotid (HE, ob. ×6)

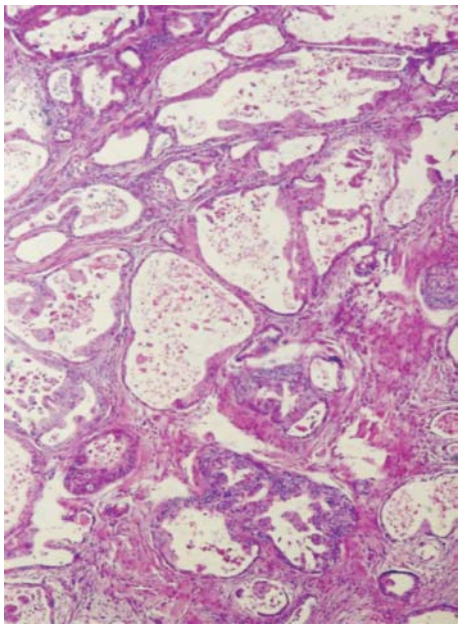

Figure 2 – Cystadenocarcinoma of parotid (HE, ob. ×6)

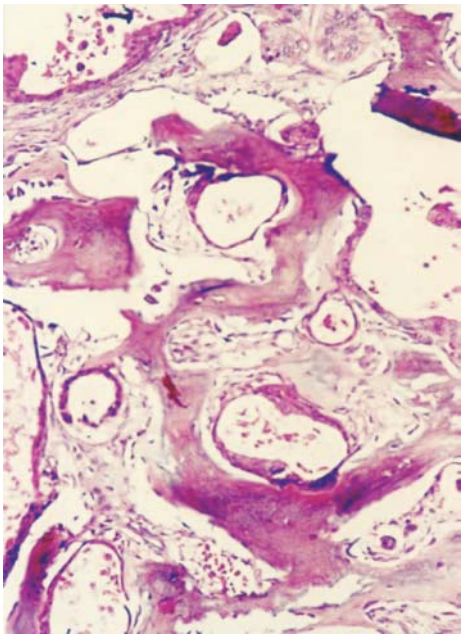

Figure 3 – Cystadenocarcinoma of parotid, osseous invasion (HE, ob. ×6)

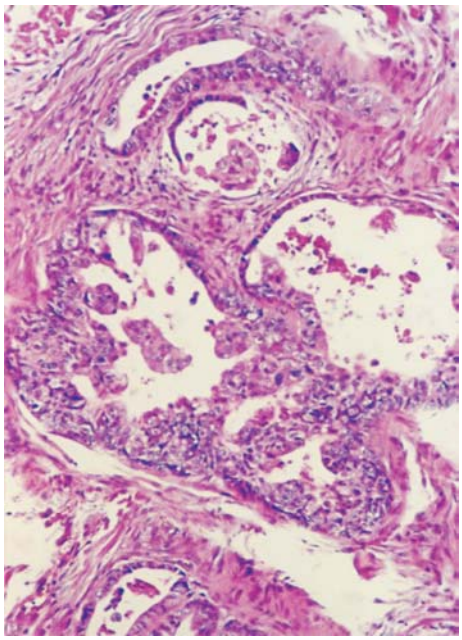

Figure 4 – Cystadenocarcinoma of parotid, mucinous and squamous metaplasia (HE, ob. ×10)

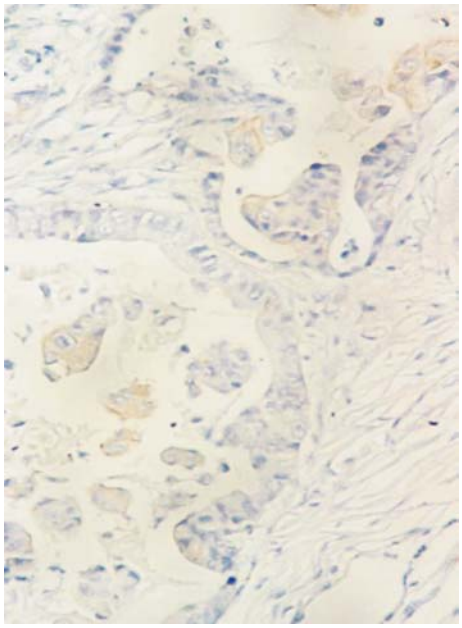

Figure 5 – Cystadenocarcinoma of parotid
(AE1-AE3, ob. ×10)

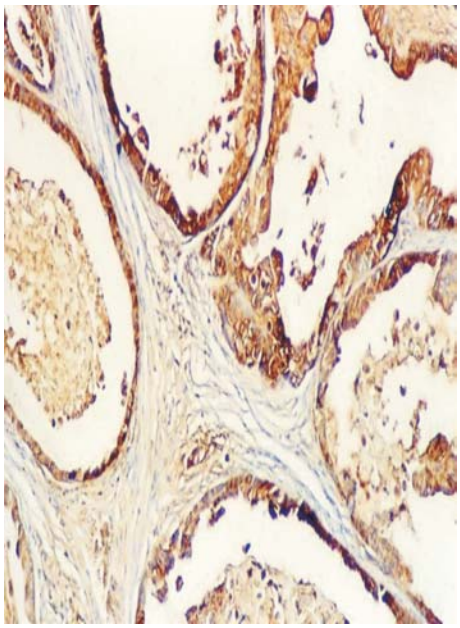

Figure 6 – Cystadenocarcinoma of parotid
(CEA, ob. ×20)

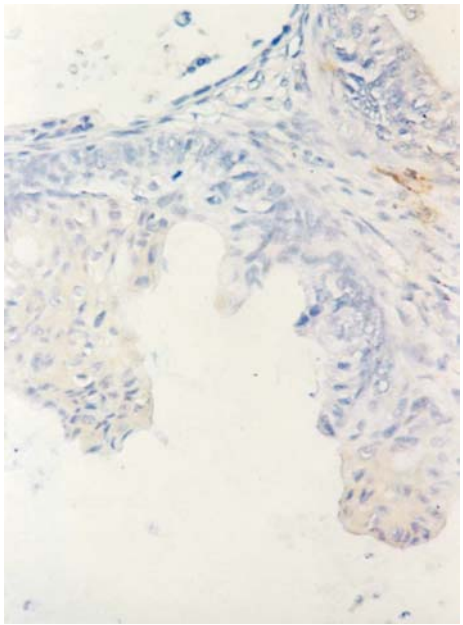

Figure 7 – Cystadenocarcinoma of parotid
(S100, ob. ×20)

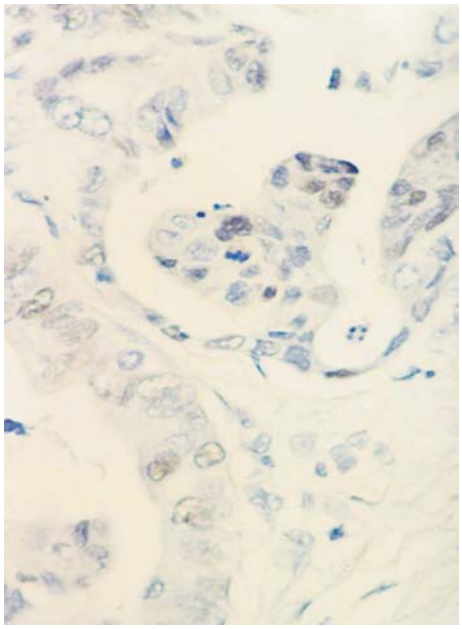

Figure 8 – Cystadenocarcinoma of parotid
(PCNA, ob. ×40)