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LETTER TO THE EDITOR

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Epstein–Barr-positive lymphoepithelial carcinoma and epi-myoepithelial cell carcinoma of the parotid gland: a hitherto unreported example of hybrid tumour

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Sir, the term "hybrid tumour" of the salivary glands has been proposed by Seifert and Donath [11] to define a tumour consisting of two histologically distinct entities that arise in the same nodule. Hybrid tumours of the salivary glands are rare, accounting for less than 0.1% of all the salivary gland neoplasms [3, 4, 7, 9, 11, 12, 15]. Several histological combinations are reported, including acinic cell carcinoma, salivary duct carcinoma, adenoid cystic carcinoma, epithelial–myoepithelial carcinoma, basal cell carcinoma, myoepithelial carcinoma, mucoepidermoid carcinoma and polymorphous low-grade adenocarcinoma [9].

We describe an Epstein–Barr virus (EBV)-positive hybrid tumour of the parotid gland composed of epi-myoepithelial carcinoma and lymphoepithelial carcinoma, arising in a Caucasian woman. The patient presented with a slowly growing mass in the right parotid gland. At physical examination, no signs of facial nerve paralysis or oropharyngeal lesions were noted. The patient underwent a right total parotidectomy with upper latero-cervical lymph-node dissection. Grossly, the resected specimen consisted of the right parotid gland, 7 cm in greatest axis, and the surrounding soft tissue. On cut surface, the gland contained a well-circumscribed, firm, greyish nodule measuring 4 cm in greatest axis. Several lymph nodes were identified in the adjacent adipose tissue.

Histologically, the tumour had a lobular appearance and was composed of nests and lobules of neoplastic cells immersed in a dense lymphoplasmacytic infiltrate, with germinal centre formation. At a higher power, it became evident that the tumour was constituted by two components intermingled without a clear-cut separation (Fig. 1).

The first component consisted of small nests and glands with a distinct pattern. Neoplastic cells were dis-

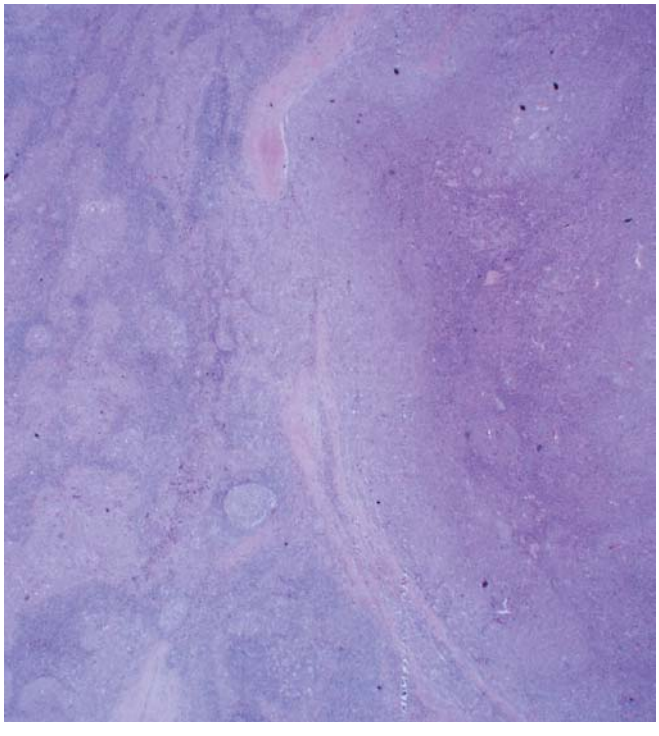

Fig. 1 The tumour is composed of nests and lobules of neoplastic cells immersed in a dense lymphoplasmacytic infiltrate, with germinal centre formation, with both a glandular (*right*) and a solid (*left*) pattern of growth. Haematoxylin and eosin, ×20

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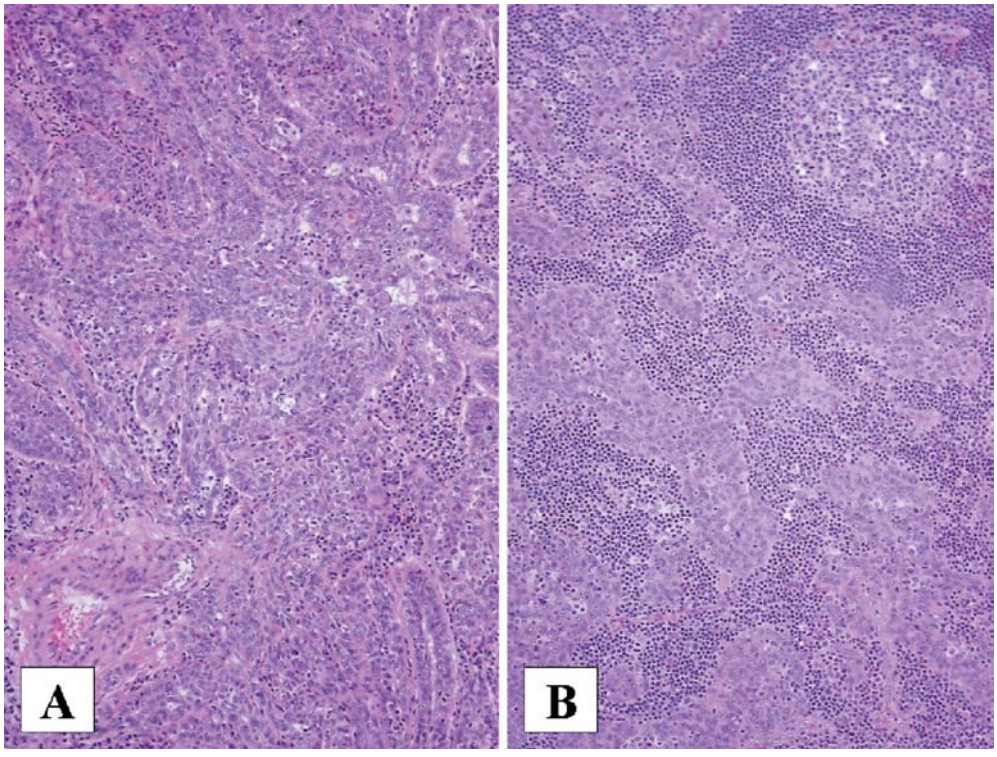

Fig. 2 At high magnification, small nests and glands (**A**) merge into irregular sheets and nests of large epithelial cells, with indistinct boundaries (**B**). Haematoxylin and eosin, ×100

posed in two layers: the outer layer was composed of cells with a small amount of cytoplasm and irregular, ovoid nuclei, while the inner (luminal) layer consisted of cuboidal cells with eosinophilic abundant cytoplasm and vesicular nuclei (Fig. 2A). Neoplastic glands and nests were closely packed, giving this component a solid appearance at low power. Mitoses were rare, and no areas of necrosis were evident.

The second component consisted of irregular, sometimes solid, sheets of large epithelial cells, with indistinct boundaries. Neoplastic cells were polygonal to spindle shaped and had abundant eosinophilic cytoplasm. Nuclei were large and vesicular, with prominent nucleoli (Fig. 2B), and mitoses were numerous. Single cell necrosis was evident.

The surrounding salivary tissue was compressed but unremarkable. There was no evidence of a pre-existing benign neoplasm, and no features of benign lymphoepithelial lesions were evident. Two regional lymph nodes contained metastatic deposits, entirely composed of the second component. Immunohistochemically, cytokeratin 14 stained neoplastic cells in both the components: in the glandular one, this antibody highlighted the bilayered pattern of the glands, as the staining was mainly localised to the outer layer (Fig. 3A, right). In the solid component, the same antibody stained approximately 20% of the cells without any specific pattern (Fig. 3A, left). Cytokeratins 7 and 19 selectively stained the inner luminal cells in the first component (Fig. 3C), while, in the second component, only rare cells were weakly stained. Smooth-muscle actin and the other myoepithelial markers (p63, myosin, calponin and S100 protein) stained the outer cell layer in the glandular component and a variable proportion of cells in the solid component (Fig. 3B). In situ hybridisation for Epstein–Barr encoded RNA revealed the presence of EBV in almost all tumour cells. The staining was more intense in the large cells of the solid component (Fig. 4A). However, both the inner (luminal) and the outer layer cells of the glandular component were stained (Fig. 4B). Adjuvant radiation therapy was administered. The patient is well without evidence of tumour 6 months after surgery.

The recognition of the most aggressive component in hybrid carcinomas is crucial, as several reports suggest that the clinical behaviour is determined by the higher grade component [4, 7, 11]. In the present case, a tumour with morphological and immunohistochemical features of epithelial–myoepithelial cell carcinoma merges with a poorly differentiated neoplasm consistent with lymphoepithelial carcinoma. Moreover, both the two components are positive for EBV with an in situ hybridisation technique.

Epithelial–myoepithelial carcinoma is an uncommon malignant tumour, which accounts for about 1% of salivary gland neoplasms [5]. In hybrid carcinomas, it has been reported in association with adenoid cystic carcinoma, salivary duct carcinoma and mucoepidermoid carcinoma [9]. Chetty et al. [3] correctly stated that adequate tissue sampling in a low-grade neoplasm, such as epithelial–myoepithelial carcinoma, may disclose a more aggressive component, and, therefore, the patient management has to be modified.

Lymphoepithelial carcinoma is an equally rare malignant neoplasia and accounts for approximately 0.4% of

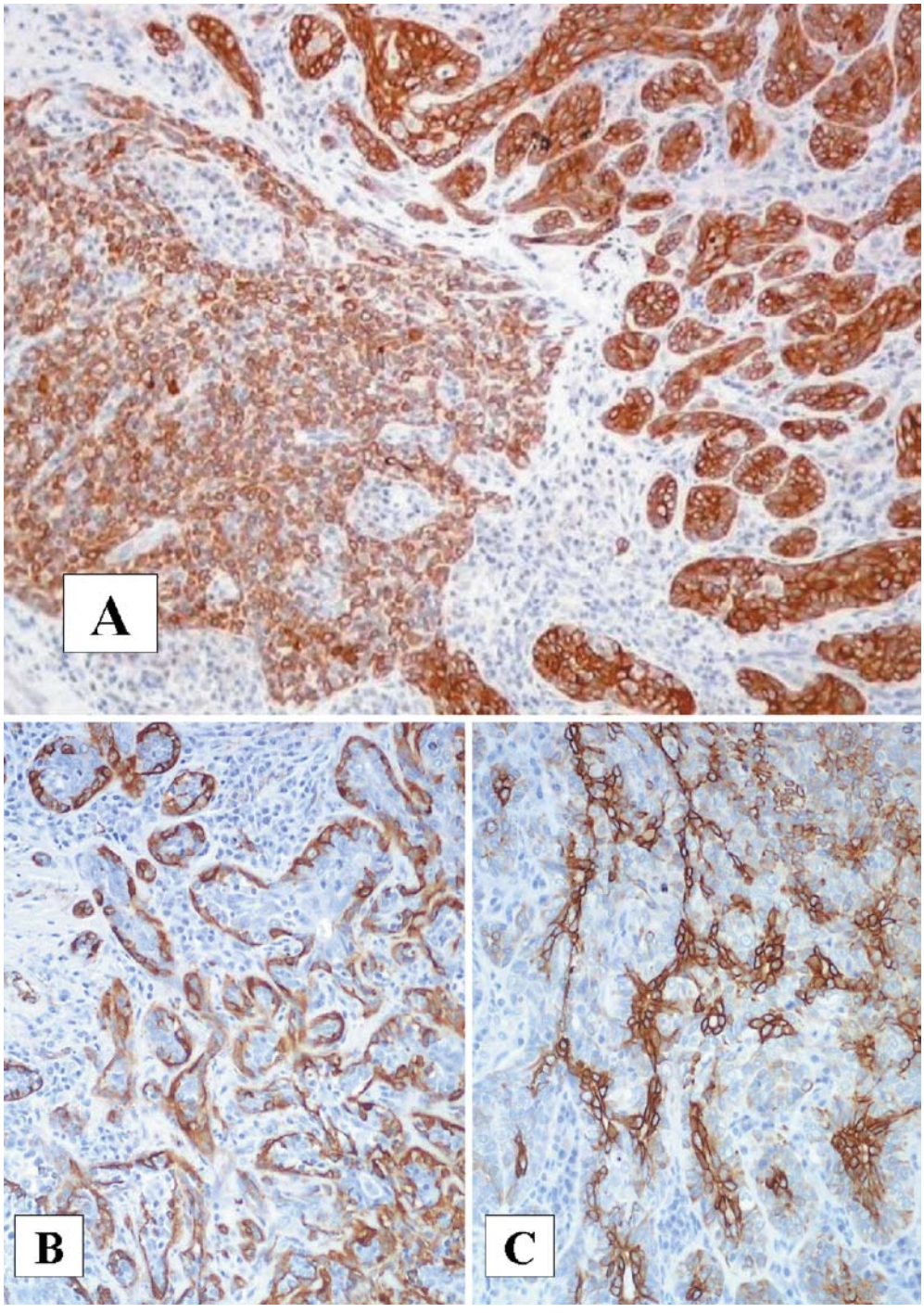

Fig. 3 A Cytokeratin 14 highlights the bilayered pattern of the glands (*right*) in the glandular component and the diffuse growth pattern in the solid component (*left*), ×100. **B** Smooth-muscle actin stains the outer cell layer of the glandular component, ×200. **C** Cytokeratin 7 stains selectively the inner, luminal cells, ×200

the salivary gland tumours [5]. It occurs almost exclusively in major salivary glands, with very few exceptions [13], and shows a higher incidence in the Eskimo and Southern Chinese population, while Caucasian patients represent less than 15% of the total cases [5]. EBV has been extensively studied as a possible causative agent, due to the striking morphological similarities with the lymphoepithelial carcinoma of the nasopharynx [1, 2, 6, 8, 10, 13, 14].

While it is common knowledge that nasopharyngeal lymphoepithelial carcinoma is very frequently associated with EBV infection in any site of the globe, with no racial preference, a consistent association with EBV in lymphoepithelial carcinoma arising in other sites, including salivary glands, has been demonstrated mainly in Eastern patients [2]. Nevertheless, some cases of EBV-positive lymphoepithelial carcinomas have also been reported in non-endemic areas [14].

The present case appears to be unique for several features: first, the finding of EBV mRNA in salivary gland tumours is quite rare in Caucasians and, to the best of our knowledge, has never been reported in a tu-

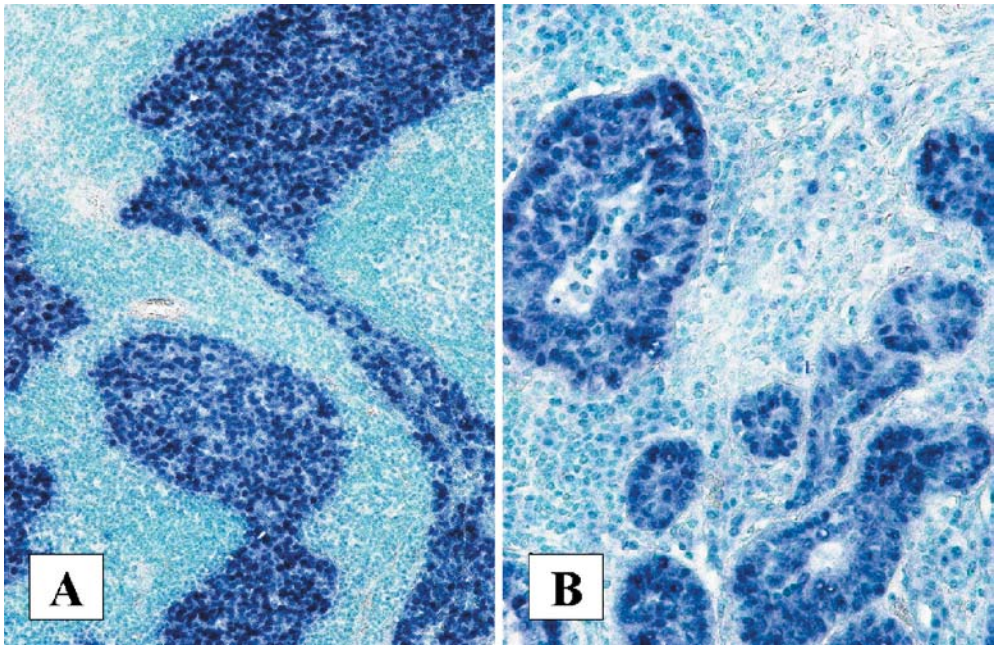

Fig. 4 In situ hybridisation for Epstein–Barr encoded RNA reveals the presence of Epstein–Barr virus either in the solid component (**A**) or in the glandular component (**B**), ×200

mour with myoepithelial differentiation. In addition, the association between lymphoepithelial carcinoma and a tumour with myoepithelial differentiation has never been recorded, and these findings open new possible pathways to the understanding of salivary gland malignancies. Finally, in our case, the lymphoepithelial carcinoma appears to be responsible for the clinical course of the disease, as lymph-node metastases were entirely composed of this tumour type. Therefore, the possible association between epithelial–myoepithelial carcinoma and lymphoepithelial carcinoma has to be kept in mind when dealing with a epimyoepithelial tumour, particularly if a lymphoplasmacytic stroma is present, in order to avoid erroneous diagnoses.

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