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Intraoral Lymphoepithelial Carcinoma of the Minor Salivary Glands

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Abstract. *The occurrence of lymphoepithelial carcinoma in the oral cavity is extremely rare and a case with involvement of minor salivary glands is very uncommon. We describe a case of LELC of the oral cavity with involvement of the upper lip and of minor salivary glands. The tumour was described at the clinical and instrumental level; moreover, its histopathological phenotype was defined. Finally, the problems of differential diagnosis and the most appropriate therapeutic approaches are discussed.*

Lymphoepithelial carcinoma (LEC) is a tumor morphologically similar to the most frequent nasopharyngeal carcinoma (NPC). This tumor presents as a more or less undifferentiated cell carcinoma accompanied by richly lymphocyte and plasma-cell infiltrates as pathological characteristic findings; moreover, both LEC and NPC have been associated with Epstein-Barr virus (EBV) infection (1).

In the literature there are many synonyms for these tumors: Regaud-type lymphoepitelioma; Schmicke-type lymphoepithelioma; undifferentiated carcinoma with lymphoid stroma, anaplastic carcinoma, transitional cell carcinoma, lymphoepithelioma, lymphoepithelioma-like carcinoma and others (1, 2).

LELC has very low metastatic potential (1, 3). This neoplasm has been described in many organs outside of the nasopharynx, such as the oral cavity, larynx, lung, thymus, stomach, uterus, urinary bladder, and skin (1). It has a characteristic geographical and ethnic distribution, being more frequent among Eskimos, Arctic people, Chinese, and Japanese (1, 4). Interestingly, in these populations constant serological and pathological evidence of EBV infections are found. Indeed, a genetic susceptibility with an association between EBV-tumors and HLA-A2 in the Chinese population in Singapore has been demonstrated. Nevertheless, this association is lacking or is not clearly demonstrated in other ethnic groups. EBV was discovered in 1964 in cultured lymphoma cells and referred to Burkitt's lymphoma in tropical African areas (3, 5). It is a member of the Herpes virus family, called human herpes virus 4, and is the etiologic agent of mononucleosis (2, 5). The genesis of EBV-related tumors seems to be associated with the action of some EBV proteins. Indeed, EBNA-1 viral protein is able to cause malignant transformation of lymphoepithelioma cells in vitro. Latent membrane protein-1 (LMP-1) is expressed during the infection phase of EBV and responsible for the suppression of T-cell activity, can determine epidermal hyperplasia and reduction of squamous differentiation (6). ZEBRA is the protein responsible for activation of the viral genome and induction of the lytic cycle (4). Finally, the transformation from the non-lytic cycle to lytic is induced by LMP2A, which increases epithelial cell migration, invasion and metastasis (7). Serological tests reveal that EBV infection is ubiquitous, but cannot be considered a reliable marker for EBV-related tumors (4). The relation between EBV infection and development of LELC is not constant. There is a site predisposition, almost a dependence, for EBV-related LEC in salivary glands, stomach, lung, thymus (7, 8).

Intraoral LEC is a very rare tumor (0.2-2% of all oral and nasopharyngeal malignant tumors), often arising in the major salivary glands and, above all, in the parotid (1, 2, 7). Indeed, there are very few cases described in the literature (1, 4, 6-11). There is a male preponderance (about 2:1) and adults are more affected in the fourth to fifth decade. In the oral cavity the most involved sites are tonsils and buccal mucosa with regard to Waldeyer's lymphatic tissue, tongue base, soft palate, floor of the mouth, retromolar area and more rarely the upper and lower lip (1, 7, 12); for the salivary glands, the parotid is affected in 80% of cases and LEC accounts for 1% of all salivary carcinomas, while the involvement of minor salivary glands is very rare (1). Recently, it has been demonstrated that patients with NPC could be distinguished on the basis of their immune status into two groups, showing more or less immune tolerance to EBV infection (13).

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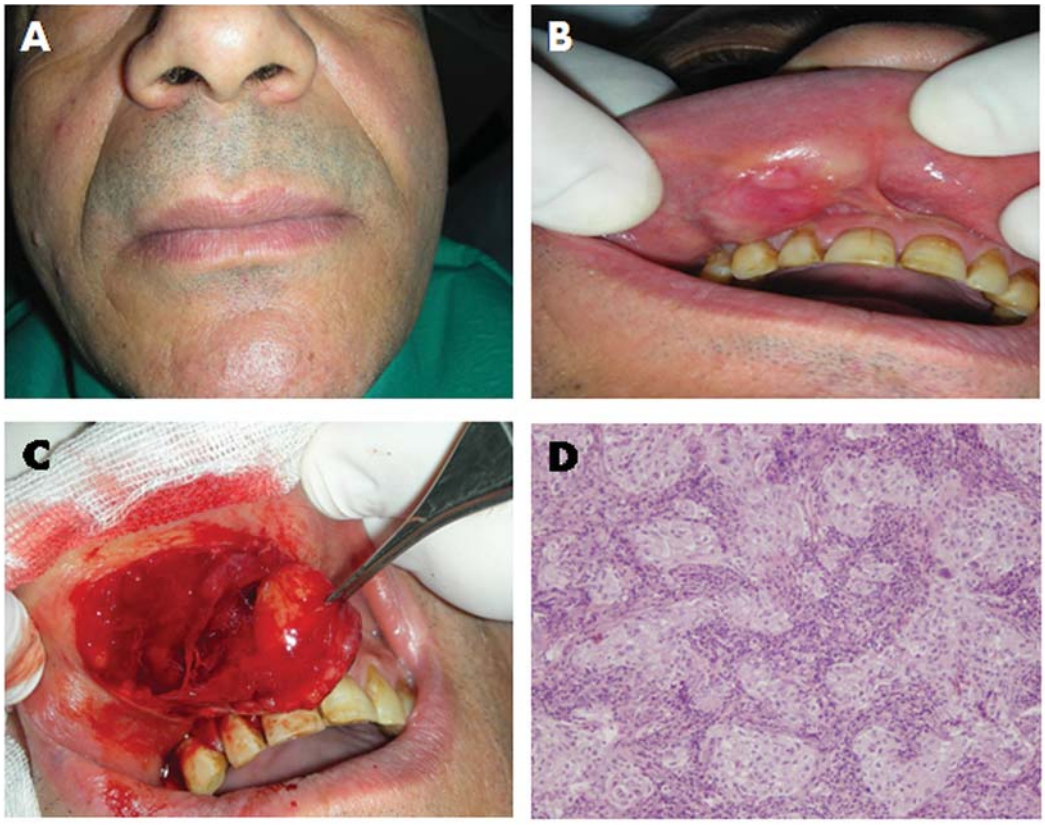

Figure 1. *A: Clinical finding of the tumor; B: intraoral aspect of the tumor; C: intra-operative step; D: histological appearance of the tumor, where both the carcinomatous component and the lymphoid stroma of the tumor are clearly visible (hematoxylin and eosin staining; original magnification, ×20).*

Case Report

A 56-year-old Caucasian man was referred to the Oral Surgery Department of the School of Dentistry of the Second University of Naples for examination and treatment of a mass in the mucous surface of the upper lip, that had swollen gradually during the previous two months. There was no other relevant past medical history, and routine blood examinations did not reveal any significant data.

On clinical examination (Figure 1A), the tumor measured 2.5×1.0 cm in diameter and exhibited hyperemic overlying mucosa without ulceration (Figure 1B); no pain was referred. The tumor was hemispherical, well-circumscribed, elastic and indolent; however, the patient declared a bad practice of lip-sucking and lip-biting. The X-ray did not show abnormality of the maxilla. Lymph nodes were not involved. Computed-tomography was negative for other sites of disease. The ultrasonography revealed an encapsulated mass with regular aspects. EBV serology was negative.

Surgical treatment of the tumor was chosen. Under local anesthesia, the tumor was entirely removed (Figure 1C), with a margin-free region of about 3-5 mm, and with reconstruction of the mucosa of the lip by a flap and 2-0 silk suture. Histologically, the tumor was made-up of nests and cohesive sheets of undifferentiated carcinoma mixed with a lymphoid stroma (Figure 1D). The carcinomatous cells were undifferentiated large cells forming syncytial sheets, with large nuclei and prominent nucleoli. Mitotic figures and individual tumor cell necrosis were also identified. Immunohistochemical staining for EBV antigen (LMP-1) was negative (data not shown). The patient was discharged on post-operative day 3 with no reported complications.

The surgical wound healed in two weeks with normal scarring. The patient remains tumor-free after two years. Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Discussion

In the oral cavity, LEC forms a painless submucosal mass that growths slowly (1, 4, 8). Sometimes, there is contemporaneous regional lymph node involvement. The radiological aspect is a located mass that respects bone layer and anatomical fascias. Ultrasonography is particularly

useful for superficial lesions to differentiate inflammatory from neoplastic lesions.

The histopathology of LEC of the oral cavity shows a well-circumscribed nodule and the features are indistinguishable from the aspects of the NPC counterparts. Often the epithelial surface may be intact. A principal component of the tumor mass is an infiltrate rich in lymphocytes and plasma cells, so diffuse that it may be defined as lymphoid stroma. The lymphoid infiltrate is sometimes so copious that the epithelial component seems absent. Poorly-visible findings are infiltrates of histiocytes which can lead to a special appearance (so-called starry sky), multi-nucleated giant cells, and amyloid depositions. If eosinophil cells are numerous, the differential diagnosis from localized eosinophilic granuloma and Langerhans cell histiocytosis must be performed (4, 8, 14).

Neoplastic lymphoepithelioma epithelial cells are polygonal and eosinophilic, with marked atypia, pleomorphism and abnormal form; sometimes the cell borders are indistinct with syncytial features; there is poor evidence of necrosis, the nuclei are vesicular and nucleoli evident. Cancer cells may be marked by pan-cytokeratin and antigens of epithelial membrane.

Differential diagnosis for intraoral LEC is made by biopsy to exclude squamous carcinoma (with a lymphoid stroma) or other local tumors such as adenoma; when the histological appearance reveals findings of limphoepithelioma, NPC must be excluded by radiological, pathological and serological examinations (4, 8).

The therapy for LEC is surgical excision. Relative treatments, such as neck dissection, radiotherapy and chemotherapy (for distant metastasis) depend on oncological evaluation. Recurrence (about 3-5% locally and 20% distant) (1) and prognosis are strongly related to tumor stage and, therefore, combined therapy is indicated in cases of high-grade pleomorphism and very high mitotic activity.

Surgical treatment in the presence of a tumor of small size and in the absence of any metastasis (stage T1-2, N0, M0), can be an effective therapy. If the resection margins are positive for LEC or a tumor has a high grade of malignancy, post-operative radiotherapy is required (1).

LEC is a variant of undifferentiated carcinoma that has been very rarely described in minor salivary glands of the oral cavity (11), such was the case for the tumor presented in this report. Therefore, LEC must be considered in the differential diagnosis when considering tumors arising from minor salivary glands.

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