

## Primary lymphoepithelial carcinoma of the parotid gland in a North African woman

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### Abstract

Lymphoepithelial carcinoma of the salivary glands is a rare neoplasm that is characterized by a non-neoplastic lymphocytic infiltration associated with an epithelial proliferation. It involves mainly the parotid gland. Racial and geographical factors contribute to the pathogenesis of this tumor. We report a case of a 70-year old woman from a non-endemic area who presented with several months history of swelling in the parotid region. Magnetic resonance imaging showed a parotid mass suggestive of a pleomorphic adenoma. The diagnosis of lymphoepithelial carcinoma of the parotid gland was performed on the surgical specimen. A primitive nasopharyngeal carcinoma was ruled out by random biopsies of the nasopharynx mucosa. The Epstein-Barr virus (EBV) was absent in neoplastic cells. We insist that, even in non-endemic areas and when clinical and radiological characteristics are not suggestive of malignancy, intra-operative frozen section analysis should be used in order to ensure the appropriate treatment.

### Introduction

Lymphoepithelial carcinoma (LEC) is a specific subtype of undifferentiated carcinoma with characteristic dense lymphoid stroma. The most frequent location is the nasopharynx. Identical tumors have been rarely described in the major salivary glands where they account for approximately 0.4% of all malignant salivary gland tumors.<sup>1</sup> A limited number of cases were reported from non-endemic areas. We report a new case from a non-endemic region with an atypical clinical presentation and an aspecific radiological pattern and we discuss the clinical and pathological pattern and management of this uncommon tumor.

### Case Report

A 70-year old women presented with a left sided, slowly enlarging, painless, non-tender mass in the parotid region of several months' duration. Her medical and surgical history was otherwise uneventful. On physical examination, in the left parotid gland she had a voluminous mass of 7 cm with a regular border that was mobile on the superficial and deep planes, and did not hurt upon palpation. Her facial nerve function was intact, and no enlarged cervical lymph nodes were palpated. The remaining systemic examination did not reveal any coexistent lesions. Magnetic resonance imaging detected a 7x6x6 cm mass in the superficial lobe of the left parotid that was interpreted as most likely representing a pleomorphic adenoma (Figure 1). The patient underwent a left parotidectomy, and the facial nerve was left anatomically intact. Her recovery was uneventful. Macroscopically, there were multiple surgical specimens that were brownish and firm in consistency. Histological findings demonstrated a tumor located in the parotid gland that was made of irregular sheets, islands and strands of poorly differentiated carcinoma richly infiltrated by lymphocytes and plasma cells, accompanied by large lymphoid follicles (Figure 2). The epithelial component consisted of large cells with indistinct cell borders resulting in syncytial appearance, eosinophilic cytoplasm and oval vesicular nuclei (Figure 3). The nuclei contained open chromatin material with prominent nucleoli. Frequent mitotic figures were also found. Areas of squamous differentiation were noted. The surrounding parotid tissue showed a chronic lithiasic sialadenitis. Immunohistochemically, most of the tumor cells were positive for cytokeratin (Figure 4).



Figure 1. Magnetic resonance imaging showing a well circumscribed mass of the left parotid gland.

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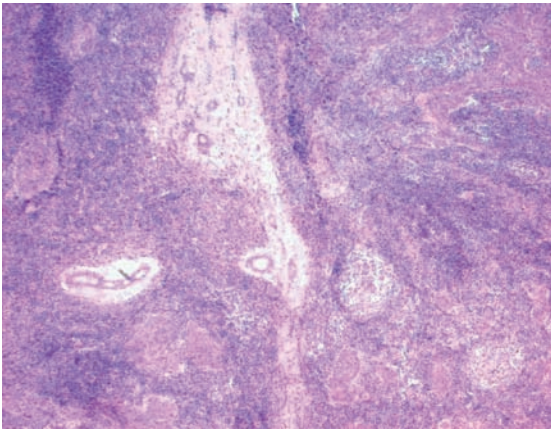
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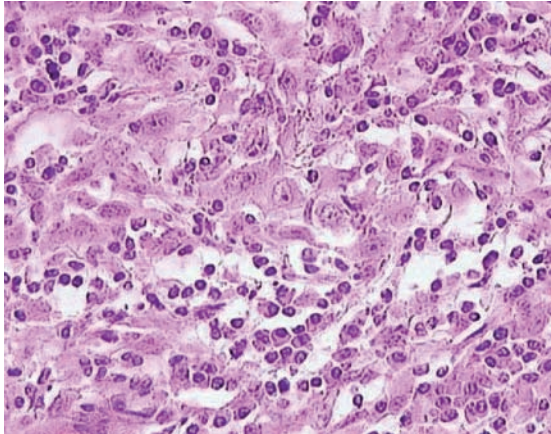
The surrounding cellular infiltrate were a mixture of CD20 and CD3 positive B and T lymphocytes. Immunohistochemical expression of EBV latent membrane protein 1 (LMP1) and in situ hybridization to EBV encoded RNA were negative. These findings were consistent with the diagnosis of primary LEC of the left parotid gland after excluding metastatic nasopharyngeal undifferentiated carcinoma to the parotid gland by random biopsies from the nasopharyngeal mucosa. The patient underwent an ipsilateral radical neck dissection and there were no lymph node metastases. She remains alive and disease free five months after treatment.

### Discussion

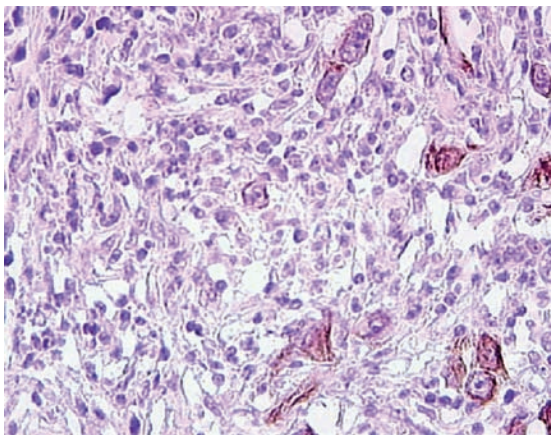
According to the classification by Ellis and Auclair,<sup>2</sup> undifferentiated carcinomas of the salivary glands can be subtyped further into



**Figure 2. Lymphoepithelial lesion of the parotid gland (hematoxylin-eosin, original magnification  $\times 40$ ). Islands of neoplastic epithelial cells (arrows) associated with lymphoid infiltration that occasionally form lymphoid follicles.**



**Figure 3. The epithelial component of the lesion have a syncytial appearance and shows an obvious pleomorphism (hematoxylin-eosin, original magnification  $\times 400$ ).**



**Figure 4. Immunohistochemical expression of cytokeratin ( $\times 400$ ).**

small cell undifferentiated carcinoma, large cell undifferentiated carcinoma, and LEC. LEC accounts for approximately 0.4% of malignant salivary gland tumors and has a characteristic extensive and dense lymphoid stroma.<sup>1</sup> This tumor affects the parotid gland in approximately 80% of the cases.<sup>3</sup> Most cases occur in the fifth decade of life and a predilection for female patients is reported.<sup>4</sup> There is a racial prevalence in Inuits (Eskimo) in the Arctic region, south-eastern Chinese and Japanese. Most parotid LEC cases arise *de novo*, but they may rarely develop within lymphoepithelial sialadenitis.<sup>5</sup> The exact origin and pathogenesis of parotid LEC

remains unknown. Among the possible etiologies are a malignant transformation of the glandular and ductal inclusions in the intraparotid lymph nodes<sup>6</sup> and a malignant transformation of the epi-myoeithelial island.<sup>7</sup> In 1991, the presence of EBV was detected by Hamilton-Dutoit *et al.*<sup>8</sup> in the malignant cells of salivary LECs in the Eskimo population of Greenland. Only a few cases of EBV-negative LEC have been reported, and almost exclusively in non-Inuit patients<sup>6</sup> suggesting that the virus plays a role in the etiology of LEC. The association of EBV with salivary gland LEC may also exist in non-endemic areas.<sup>4</sup> It seems there is a complex interaction between

genetic factors, environmental factors, and EBV infection in the oncogenic process of LEC of the salivary glands.<sup>9</sup> Parotid LEC usually presents as an enlarging parotid lump, occasionally painful and with facial nerve involvement in approximately 20% of cases.<sup>4</sup> Clinical features suggestive of malignancy are rapid-growing course, pain or tenderness, progressive facial nerve palsy and obvious cervical lymphadenopathy.<sup>10</sup> Our case is particular for the atypical presentation suggesting a benign lesion; in fact, our patient showed no signs suggestive of malignancy. On presentation, up to 40% of patients have metastases to the cervical lymph nodes, 20% develop local recurrence or lymph node metastases, and 20% have distant metastases within three years following therapy. Distant metastases usually involve the lung, liver, bone, and brain.<sup>1</sup> Macroscopically, these tumors are firm, 1-10 cm masses, multinodular, circumscribed, or clearly infiltrative into adjacent salivary gland, fat, muscle, or skin, with a cut surface that varies from a grey-tan to yellow-gray.<sup>11</sup> Histologically, it is characterized by a syncytial growth pattern and a dense stroma made of non-neoplastic lymphoplasmacytic cells; the lymphoid cells include a mixture of B and C cells and are sometimes associated with germinal centers. The epithelial component is composed of irregular shaped islands, cords, trabeculae of pleomorphic, large, malignant cells with abundant lightly eosinophilic cytoplasm and vesicular nuclei.<sup>3,12</sup> Mitotic rate is variable. Histiocytes are abundant in the tumor islands in some cases, imparting a 'starry sky' appearance.<sup>3</sup> Other inconsistent findings are non-caseating granulomas with or without multinucleated giant cells and amyloid deposition.<sup>13</sup> A definite squamous differentiation with intercellular bridges has been identified in several cases.<sup>3</sup> LEC is indistinguishable from undifferentiated nasopharyngeal carcinoma which is much more common or other LECs that develop in various parts of the body.<sup>4,10</sup> Therefore, to confirm the diagnosis of primary LEC in the major salivary glands, metastatic nasopharyngeal carcinoma to the salivary glands should be eliminated through examination of the upper aerodigestive tract with endoscopy and even random biopsy of the nasopharynx.<sup>3,4,10,13</sup> In reality, the parotid gland is the predominant site of occurrence of LEC and an exceptional site of metastasis from nasopharyngeal carcinoma, which more typically metastasizes to the cervical or submandibular lymph nodes.<sup>1</sup> Histologically, the LEC must be distinguished from benign lesions such as lymphoepithelial sialadenitis and from other epithelial malignancies, such as primary or metastatic poorly differentiated squamous cell carcinoma, adenocarcinoma, and amelanotic melanoma; another differen-

tial diagnosis is with large cell or anaplastic types of lymphoma.<sup>2</sup> The optimal management of LEC of the major salivary glands is complete excision with clear surgical margins followed by adjuvant radiotherapy to the tumor bed and neck.

Neck dissection is reserved for patients who have clinically positive cervical lymph nodes.<sup>10,14</sup> Our patient underwent only surgical treatment because radiotherapy was not available at that time. Lymphoepithelial carcinoma seems to have a better prognosis than the other undifferentiated carcinomas of the salivary glands, in part because of the lymphoid stroma that has a role in limiting the aggressiveness of this carcinoma. Advanced disease, the presence of metastases on diagnosis, and histological features such as high mitotic rate, anaplasia, and necrosis are predictors of a worse prognosis.<sup>1,9</sup> The 5-year survival rate has been reported to range from 50-87%.<sup>10</sup>

In conclusion, it is worth underlining the diagnostic difficulty in this case caused by the absence of clinical symptoms suggestive of malignancy and the non-specific nature of the radiological signs. In order to ensure a correct therapeutic approach, intra-operative frozen section analysis of a parotid mass should be used to exclude a malignant tumor even when dealing with a clinical and radiological presentation suggestive of pleomorphic adenoma.

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