PAROTID GLAND MALIGNANCIES - DIAGNOSTIC QUERIES IN RARE SITUATIONS: REPORT OF TWO CASES

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Abstract: *Parotid malignancies are a heterogeneous group of diseases that include 23 entities, all of epithelial origins. Non-epithelial tumours are rare, representing about 2-5% of all salivary gland tumours. Primary lymphatic tumours of the parotid are even rarer. The clinical appearance usually includes a variable history of slow growing painless, nodular mass that enlarges rapidly. The cytological evaluation should identify whether the parotid lesion is inflammatory or neoplastic, and if it is malignant or benign. On diagnosis of a salivary gland tumour, it is important to correctly classify the tumour especially if malignant in order to apply the correct treatment. There are presented two cases of rare malignant entities with lymphoid component located on parotid gland which presented difficulties in preoperative diagnosis.*

INTRODUCTION

The parotid glands are the largest human salivary glands and sometimes, they are involved in tumour formation processes. Approximately 25% of parotid masses are non-neoplastic; the remaining 75% are neoplastic. Approximately 80% of parotid neoplasms are benign.(1)

In terms of histology, parotid are exocrine glandular organs that produce and secrete saliva and are formed of ducto-acinar units containing four cell types: ductal, acinar, myoepithelial and basal.(2,3,4,5)

World Health Organization (WHO, 2005) classified salivary gland tumours into 10 benign and 23 malignant entities all of epithelial origin. Non-epithelial neoplasms are very rare representing about 2-5% of all salivary gland tumours.(6,7) Primary lymphatic tumours are even rarer and difficult to be diagnosed.

The etiology of salivary gland tumours is still unclear. However, it is presumed that smoking, viral infections, genetic predisposition could have a part in tumour formation at this level.(2,7)

The initial preoperative evaluation of parotid tumours begins with a careful history, followed by thorough clinical examination of the face and neck, imaging explorations (especially ultrasonography and computed tomography) and fine-needle aspiration which provides a sample of tumour tissue for cytology assessment. In most cases, the cytological aspect can indicate a specific diagnostic, but in some particular situations definitive diagnosis remains the histological one.(5)

However, fine-needle aspiration has some limits and many challenges in cases of rare entities, overlapping histologic features and malignant tumours with benign equivalents.(8)

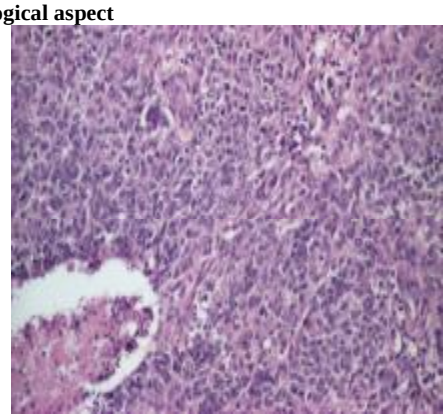
CASE REPORTS

Case 1.

A 66-year-old male patient presented facial asymmetry and a painless mass in his right parotid area. He reported that the mass had been slowly enlarging for about one year with accelerated growth in the last 4 months. On examination, there was a 5 cm diameter, firm, irregular mass arising in the right pre-auricular region, which appeared to be fixed to the deeper tissues. The overlying skin was adherent on the tumour. Clinically, there was no involvement of the facial nerve.

Ultrasonography was performed and it showed a right parotid hypoechogenic mass with irregular contour, heterogeneous, well vascularised, of about 40x33 mm and two nodular hypoechogenic superficial lesions up to 5 mm. Computed tomography revealed the same tumour location with no other head and neck tumours and no lymph node involvement. Fine needle aspiration cytology described atypical epithelial cells with large, hyperchromic nuclei among many lymphocytes, in a background of necrotic debris and histiocytes with foamy cytoplasm that corresponded to an undifferentiated carcinoma. Under general anaesthesia, the patient underwent total parotidectomy and right selective neck dissection.

Figure no. 1. Undifferentiated lymphoepithelial carcinoma. Histological aspect



Histology (figure no. 1) revealed the tumour was formed of large clusters of cells with indistinct margins and syncytial appearance. The tumour cells presented reduced

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cytoplasm, large, vesicular nuclei, prominent nucleoli and numerous atypical mitoses. In the centre of cell islands necrosis occurred, and around them there was an abundant inflammatory infiltrate. Small lymphocytes were found between tumour cells. At the tumour periphery, residual parotid parenchyma appeared infiltrated. Inside the parotid gland, there were found two non-metastatic lymph nodes, one lymph node with tumour metastasis and another with direct tumour invasion. There was also found lymphovascular and perineural invasion. On immunohistochemical examination, tumour cells were positive only for Cytokeratin AE1/AE3 being negative for Cytokeratin 5/6 and Cytokeratin7, p63, SMA, PS100, chromogranin and Sinaptophyzin. The diagnosis was *undifferentiated lymphoepithelial carcinoma.*

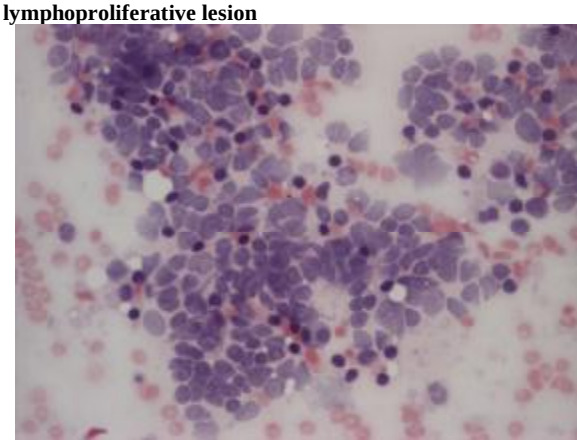
Postoperatively the patient followed oncologic radiotherapy and chemotherapy.

Case 2.

A 73-year-old female patient was examined in the Maxillo-Facial Surgery clinic for a right facial painless tumour with a history of two years growing. Physical examination revealed that the mass belonged to the lower pole of the right parotid, had about 4 cm in diameter, and was firm, mobile to adjacent structures without right facial nerve involvement. The patient had no history of cancer or autoimmune diseases.

The patient underwent fine-needle aspiration of parotid tumour that indicated inflammatory cells, red blood cells and numerous monomorphic cells, atypical lymphocytes suggestive of a lymphoproliferative lesion (figure no. 2).

Figure no. 2. Cytological aspect suggestive for lymphoproliferative lesion

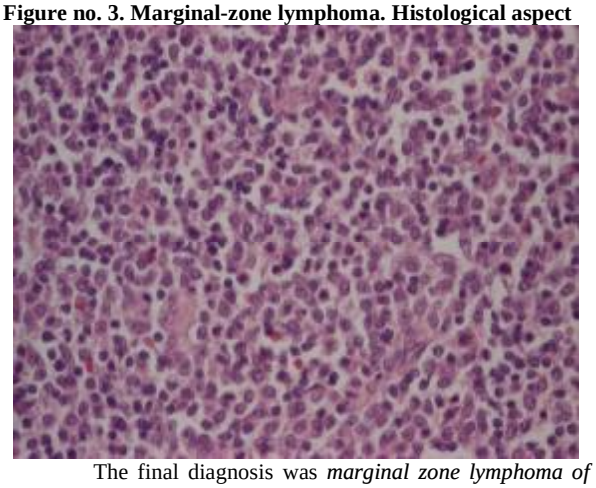


Computed tomography revealed a mass of about 31/33mm diameter at the right parotid gland, which does not come in direct contact with major vascular elements of the neck and no lymphadenopathy was identified.

Superficial parotidectomy was performed and facial nerve was preserved, surgical specimen being sent for histopathological examination. Histology revealed a lymphoproliferative process consisting of small monomorphic cells with monocytoid and plasmacytoid aspect located predominantly between follicles and in sinuses.

Immunohistochemical examination has shown that tumour cells were intense and diffuse positive for CD20. CD3 and CD5 marked surrounding reactive T lymphocytes. CD23 and CD10 showed positive reaction on the remaining centres but negative reaction for tumour cells. Bcl-2 was positive between remaining germinal centres. Ki-67 was strongly positive at the central level and 10% at the remaining tumour cells. Bcl-6, CiclinD and PanCytokeratin showed negative reaction (figure no. 3).

Figure no. 3. Marginal-zone lymphoma. Histological aspect



The final diagnosis was *marginal zone lymphoma of the right parotid*. Patient underwent oncologic treatment – chemotherapy.

DISCUSSIONS

Malignant tumours of the salivary gland have the main complaint the presence of a painless swelling that is often associated with symptoms, such as facial nerve palsy (in 10-15% of cases), pain (in 10-29% of patients) and tumour fixation on deep structures. These features indicate local or regional tumour invasion.(9)

Fine-needle aspiration is considered to have an important role in the diagnosis of salivary gland tumours and compared with excisional biopsy is easier, safer and cheaper. Virtually, any salivary gland swelling can be assessed by aspirative cytology. Some clinical studies have shown that in case of salivary gland tumours, the aspirative cytology presented a sensitivity between 60-100% and a specificity between 90-100% in the diagnosis of these lesions.(8)

In cases of rare malignant tumours that have benign, counterpart cytology can not bring enough data for proper differentiation of the two tumour variants, which can be done only on the basis of some histological hallmarks, such as their invasive outgrowth, vascular and perineural invasion, necrosis and mitosis. However, there are cases with limited samples in which the morphological appearance is not sufficient to provide a differential diagnosis between the two, requiring immunohistochemical evaluation.(3)

Salivary gland tumours present histologic variants and overlaps, requiring the use of immunohistochemistry as a helpful tool in situations that cannot be assessed only by histology, such as the cell nature and differentiation status, cell proliferation and tumour protein expression.(3)

Lymphoepithelial carcinoma represents less than 0.5% of malignant tumours of the salivary gland and is a variant of anaplastic carcinoma with characteristic dense lymphoid stroma.(10,11,12)

Clinical studies demonstrate a predilection of this entity in the population of Southeast Asia and Arctic region natives, but also a close association with Epstein-Barr virus infection.(6,10,11,12,13) It could be a secondary determination of an undiagnosed mucosal lymphoepithelial carcinoma (usually nasal).(13)

In our case, fine-needle aspiration was done as a part of per-operative investigations and showed cells suggestive of a poorly differentiated neoplasm with lymphocytes and epithelioid features without stating a certain diagnosis.

In establishing the histologic diagnosis of

lymphoepithelial carcinoma, the most important finding is the presence of lymphoepithelial nests similar to those of benign lymphoepithelial lesion.(11)

The differential diagnosis is difficult because histologic, histochemical, and ultra-structural studies cannot reliably distinguish between lymphoepithelial carcinoma and its benign counterpart. Differential diagnosis from amelanotic melanoma, large cell lymphocytic and histiocytic neoplasms is helped by immunohistochemical markers.(11)

Undifferentiated lymphoepithelial carcinoma should be differentiated from malignant lymphoma which is made on the basis of immunohistochemical reactions. Undifferentiated carcinomas are immunopositive for pan-CK and negative for leukocyte common antigen while malignant lymphoma presents the opposite immunostaining results.(3)

This tumour has a strong tendency to metastasise, first of all to the parotid nodes, then to the upper cervical and retro-auricular nodes, and later to the supra-clavicular and para-tracheal nodes. Distant metastases usually involve the lung, liver, bone, and brain.(11)

Lymphoepithelial carcinoma seems to have a better prognosis than the other undifferentiated carcinomas of the salivary glands, perhaps because of the lymphoid stroma that has a role in limiting the aggressiveness of this carcinoma.(11)

Primary lymphoma of the salivary gland represents about 4.7% of all lymphomas. Most are non-Hodgkin lymphomas and occurs in the parotid. These entities may be classified as extra-nodal if the origin is from the mucosa associated lymphoid tissue or nodal if the true origin is from lymph node within the gland.(14)

Marginal zone lymphoma of the parotid is a type of extra-nodal B-cell non-Hodgkin lymphoma, a low-grade lymphoma that appears as a painless, progressively enlarging mass.(15,16) It is considered that the most marginal zone lymphomas appear on a pre-existing lymphoid stimulation (benign lymphoepithelial lesion or Sjogren syndrome) (14,15,17), but it can also occur in patients who had no history of these conditions.(14,16)

Clinical presentation is indistinguishable from other benign parotid swellings.

Preoperative fine-needle aspiration of the involved lesion and radiological investigation which are part of the preoperative assessment of any suspicious parotid gland lesion are inconclusive. It is considered that a parotid marginal zone lymphoma is difficult to be diagnosed by fine-needle aspiration cytology.(14)

In our case, cytological data have raised suspicion of a malignant lymphoproliferative lesion, without giving other details to establish the final diagnosis. The diagnosis was indicated on examination of histopathological specimen after immunohistochemical tests, aspect supported by other authors as well.(14,15,16)

Marginal zone lymphoma diagnosis is difficult based only on histological observation, although the diagnostic criteria are still subject of controversy and no consensus exists among experts. Immunohistochemical reactions show diffuse staining of B-cell markers such as CD20 and CD79a or abnormal expression of CD43. Since this type of lymphoma is almost always negative for CD5, CD10 and cyclin D1 it can be distinguished from other B-cell lymphomas.(3)

The prognosis of marginal zone lymphoma of the parotid gland is generally better than other extra-nodal lymphomas.(14)

Fine-needle aspiration offers the surgeon the ability to risk-stratify patients, to counsel them appropriately and to avoid surgery in those cases where it is not appropriate or unnecessary. Moreover, should a benign process be suspected on fine-needle aspiration cytology, the facial nerve can be preserved safely.(18,19)

It is considered that the primary value of aspirative cytology in cases of parotid tumours is to establish the need for definitive surgery, not to establish a specific diagnosis.(18) In those situations in which cytological and clinical impressions diverge (especially in cases of rare malignant tumours), histological findings remain an important arbitrator (6), inasmuch as malignant salivary gland lesions have always been difficult to classify with fine-needle aspiration alone.(20)

The cytological opinion on a fine needle aspirate from a salivary mass should always be interpreted in the context of clinical and imaging findings.

The histopathological evaluation is the only reliable assay which can correctly identify the salivary gland rare entities and classify them accordingly. Immunohistochemistry should be considered a method that can be used to assist the final histological diagnosis, but unfortunately few tumour-type specific immunomarkers are currently available, probably due to a very low incidence of these entities.(3)

CONCLUSIONS

On account of many histological overlapping of different parotid entities and the existence of malignant counterparts of the benign tumours, it is considered that the correct final diagnosis of rare salivary gland tumours especially for non-epithelial entities is always the histopathological one.

Preoperative cytology is useful for the diagnosis triage of parotid masses, but the precise diagnosis of lymphoid tumours is difficult on limited cytological samples.

Immunohistochemistry has limited value but important for correct classification of rare tumour entities. Immunohistochemical aspects should always be considered in the context of histological morphology for the correct classification of lesions.

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