Journal of BUON **14:** 653-659, 2009

ORIGINAL ARTICLE

Fine needle aspiration cytology in the diagnosis of head and neck masses: accuracy and diagnostic problems

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Summary

Purpose: *Fine needle aspiration (FNA) cytology is an established technique associated with minimal complications compared with more invasive techniques such as wide core needle biopsy or open biopsy, and as such, very suitable for obtaining material in the delicate region of head and neck (H&N). The aim of this study was to assess the diagnostic accuracy of FNA cytology H&N masses.*

Methods: *Aspirations were performed by cytologists using 25 or 27G needles with 20 ml syringes attached, and smears were stained with May-Grunwald-Giemsa. Four hundred and ninety-four patients with palpable H&N masses underwent FNA during the study period of 2 years.*

Results: *Based on cytology alone, the most common findings were reactive lymphoid hyperplasia (28.5%), metastatic carcinoma (22.7%) and lymphoma (13.4%). Sixty-four (12.6%) FNA specimens were inadequate for diagnosis. Histological correlation was available in 164 (33.2%) patients who went on to have surgical excision of the mass. Nondiagnostic aspirate was in 16 (9.75%) patients, so the final group for cyto-histological correlation included 148 patients. The overall accuracy rate of FNA cytology, whether malignant or benign, was 91.89%, while the diagnostic accuracy for the exact type of tumor was 87.16%. There were 3 (2%) false-positive (FP) and 9 (6.1%) false-negative (FN) cytological diagnoses. The sensitivity and specificity of FNA cytology in determining a malignant diagnosis were 91.5% and 92.85%, respectively. Positive (PPV) and negative predictive value (NPV) were 97 and 81.25%, respectively.*

Conclusion: *Our results showed that FNA cytology is a simple, safe, and cost-effective diagnostic method, suitable as a first-line investigation in palpable H&N masses. The main causes of the wrong diagnoses were sampling errors, inexperience and misinterpretation.*

Key words: cytodiagnosis, fine needle aspiration, head and neck masses, histology

Introduction

Clinical evaluation of solitary H&N masses is difficult due to the delicacy of this region with vital organs and various tissues in a relatively small space, which requires the best possible, less invasive diagnostic approach.

Radiological imaging techniques, including ultrasonography, computed tomography and magnetic resonance imaging, are of great help in defining the size and extent of the mass, its relationship with surrounding tissues and organs, in detecting calcifications, vascularity and consistency, features that give very important information for accurate preoperative planning. But in some cases it can be difficult to differentiate between tumor, scar tissue, radiation edema or infection, using these techniques alone [1]. These techniques are not always able to define precisely the organ or tissue involved, nor the nature and biological potential of tumor masses.

FNA cytology is an established technique associated with minimal complications compared with more invasive techniques such as wide core needle biopsy or open biopsy, and as such very suitable for obtaining material in this delicate region. The advantage of FNA cytology is not only its non-invasive nature, but also the possibility of rapid information of the aspirated material that enables adequate management of a patient without delay.

In this article we report on our experience in FNA cytology in the diagnosis of H&N masses in 494 pa-

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Received 11-11-2008; Accepted 24-02-2009

tients, with special consideration of cytological misdiagnoses in comparison with final histology.

Methods

Over a 2-year period, FNA cytology of palpable H&N masses was carried out in 494 patients at the Institute of Pathology, Department of Cytology and Cytogenetics, Military Medical Academy, in Belgrade. FNA was performed by cytologists using 25 or 27G needles attached to 20 ml syringes, and air-dried smears were stained with May-Grunwald-Giemsa. The diagnostic accuracy of FNA cytology was assessed with histological correlation. All cytological misdiagnoses were reviewed by two senior cytologists.

Results

During the study period, in 494 patients in whom the FNA of H&N masses was performed, the most common findings were reactive lymphoid hyperplasia (28.5%), metastatic carcinoma (22.7%) and lymphoma (13.4%), followed by salivary gland tumors (5.7%), granulomatous lymphadenitis (4.0%) and congenital cysts (3.8%). Nondiagnostic cytological material was obtained in 12.6% of the cases (Table 1).

The correlation between cytological and histological diagnosis was possible in 164 (33.2%) patients. From this number of patients, the cytologic material was nondiagnostic because of scanty or acellular samples in 16 (9.75%). In the remaining 148 patients with adequate FNA, concordance between cytological and histological diagnosis in differentiating benign from malignant conditions was noted in 136 (91.89%) cases.

FP cytological diagnosis for malignancy was documented in 3 (2%) patients and FN in 9 (6.1%). Although these 3 cases were only suspicious for malignancy, we considered them as FP in the calculation of false positivity for malignancy. Sensitivity reached 91.5%, specificity 92.85%, PPV 97% and NPV 81.25%. Concordance of the diagnoses was confirmed in 129 patients, meaning that the diagnostic accuracy for the exact type of tumor was 87.16%.

The most frequent cytologic diagnosis in this group of 148 patients were metastatic carcinoma in 51 (31.1%), lymphoma in 37 (22.56%) and reactive lymphoid hyperplasia in 15 (9.15%) patients. Concordance between cytological and histological diagnosis for metastatic carcinoma is shown in Table 2. Histological correlation confirmed FNA diagnosis of squamous cell carcinoma in all 11, and small cell carcinoma in all 13 cases, adenocarcinoma in 6 cases, while one was adenosquamous carcinoma and one was cytologically misdiagnosed as squamous cell carcinoma. Out of 13 cases cytologically diagnosed as non small cell carcinoma, 4 were squamous cell carcinoma, 3 adenocarcinoma, 5 adenosquamous carcinoma and one remained non small cell carcinoma. Out of 6 cases cytologically diagnosed as poorly differentiated carcinoma 4 were squamous cell carcinoma, one adenosquamous carcinoma and one remained with the same diagnosis.

Concordance between cytological and pathological diagnosis for lymphoma and reactive lymphoid hyperplasia is shown on Table 3. Out of 15 cases cytologically diagnosed as reactive lymphoid hyperplasia, pathology confirmed 6, while 2 were Hodgkin's lymphoma (HL), 5 non-Hodgkin's lymphoma (NHL), one granulomatous lymphadenitis and one sinus histiocytosis (Figure 1). All 13 cases cytologically diagnosed as HL and 18 cases diagnosed as NHL were confirmed by histological diagnosis. One case suspicious of NHL was HL, but in 2 cases reported as suspicious for HL the final histological diagnosis was Kikuchi's disease in one and lymphoepithelioma in the other one. Three cases cytologically reported as suspicious lymphoma, without more precise determination, were HL. While accuracy for diagnosis of metastatic carcinoma was 94.5%, accuracy for lymphoid aspirates was 78.8%, and sensitivity and specificity, PPV and NPV were 83.5, 80, 94.6% and 53.3%, respectively.

There were 19 misdiagnoses in all, regarding the exact type of tumor or biological potential (benign-malignant), which is shown on Table 4. FNA cytologi-

Table 1. Cytological diagnoses in 494 patients in whom FNA of head and neck masses was performed

FNA cytology	*Number of patients*	*%*
Reactive lymph node	141	28.5
Metastatic carcinoma	112	22.7
Lymphoma	66	13.4
Salivary gland tumors	28	5.7
Granulomatous inflammation	20	4.0
Congenital cysts	19	3.8
Cystic changes	9	1.8
Necrotic material	9	1.8
Suppurative inflammation	9	1.8
Extramedullary hematopoiesis	4	0.8
Granulomatous tissue	3	0.6
Thyroid gland tumors	3	0.6
Other masses*	7	1.4
Nonrepresentative material	64	12.6
Total	494	99.5

*lipoma, schwannoma, malignant cells, hematoma, tumor of probably mesenchymal origin

Table 2. Concordance between cytological and histological diagnosis for metastatic carcinoma

FNA cytology	*Histology*						
	Squamous Ca	*Adeno Ca*	*NSC Ca*	*SC Ca*	*Adenosquamous Ca*	*Adeno anaplastic Ca*	*Poorly diff Ca*
Squamous Ca (n=11)	11	–	–	–	–	–	–
Adeno Ca (n=8)	1	6	–	–	1	–	–
NSC Ca (n=13)	4	2	1	–	5	1	–
SC Ca (n=13)	–	–	–	13	–	–	–
Poorly diff Ca (n=6)	4	–	–	–	1	–	1

Ca: carcinoma, NSC: non small cell, SC: small cell, poorly diff: poorly differentiated

Table 3. Concordance between cytological and pathological diagnosis for lymphoma and reactive lymphoid hyperplasia

FNA cytology	*Histology*						
	RLH	*HL*	*NHL*	*Granulom*	*Sinus histiocytosis*	*Kikuchi's disease*	*Lymphoepithelioma*
RLH (n=15)	6	2	5	1	1	–	–
HL (n=13)	–	13	–	–	–	–	–
NHL (n=18)	–	–	18	–	–	–	–
Susp. HL (n=2)	–	–	–	–	–	1	1
Susp. NHL (n=1)	–	1	–	–	–	–	–
Susp. Lymphoma (n=3)	–	3	–	–	–	–	–

RLH: reactive lymphoid hyperplasia, HL: Hodgkin's lymphoma, NHL: non Hodgkin's lymphoma, Granulom: granulomatous lymphadenitis, susp: suspicious

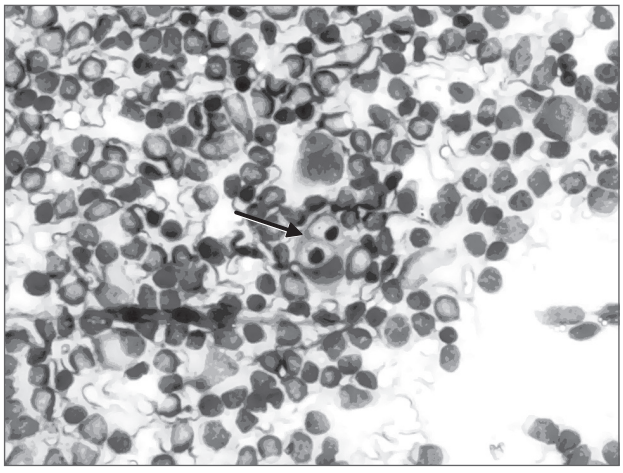

Figure 1. Sinus histiocytosis. Background of reactive lymphoid cells with histiocytes and epithelioid histiocytes, and 2 well-preserved lymphocytes (arrow) in the cytoplasm of one histiocyte (emperipolesis) (MGG ×400).

cal diagnosis for malignancy was reported in 9 cases: 2 HL and 5 NHL were reported as reactive lymphoid hyperplasia, 1 mucoepidermoid carcinoma reported as probably retention cyst - benign salivary gland duct obstruction, and 1 metastasis of papillary thyroid carcinoma reported as suspicious nodular goiter with cystic degeneration.

FP cytological diagnoses for malignancy were: colloid nodule, reported as suspicious papillary thyroid carcinoma in one, and suspicious metastasis of papillary thyroid carcinoma in another one; and Kikuchi's lymphadenitis, reported as suspicious HL. Besides FN and FP cytological diagnosis for malignancy, there were 5 misdiagnoses regarding the type of tumor: one lymphoepithelioma was cytologically reported as suspicious HL (Figure 2), 1 malignant fibrous histiocytoma was reported as extramedullary hematopoiesis

Table 4. Noncorcondance between cytological and final histological diagnosis regarding the malignancy and the exact tumor type

Cytology	*Histology*
Susp. papillary thyroid Ca*	Colloid nodular goiter
Susp. M of papillary thyroid Ca*	Colloid nodular goiter
Susp. Hodgkin's lymphoma*	Kikuchi's disease
Reactive lymph node (n=2)†	Hodgkin's lymphoma
Reactive lymph node (n=5)†	Non Hodgkin's lymphoma
Benign salivary gland obstruction†	Mucoepidermoid Ca
Hodgkin's lymphoma	Lymphoepithelial Ca
Nodular goiter with cystic degeneration†	M of papillary thyroid Ca
Extramedullary haematopoiesis	Malignant fibrous histiocytoma
Adenoid cystic Ca	M of papillary thyroid Ca
Mucoepidermoid Ca	Basal cell Ca**
Reactive lymph node	Sinus histiocytosis
Reactive lymph node	Granulomatous lymphadenitis
Granulomatous lymphadenitis	Chronic suppurative inflammation

Susp.: suspicious, Ca: carcinoma, M: metastasis
*FP and †FN for malignancy, **Review of histology confirmed the cytological diagnosis

(Figure 3), 1 metastasis of papillary thyroid carcinoma was reported as suspicious adenoid-cystic carcinoma of salivary gland (Figure 4) and one basal cell carcinoma was reported as mucoepidermoid carcinoma (Figure 5). One granulomatous inflammation was reported as reactive lymphoid hyperplasia, and 1 chronic suppurative inflammation was reported as suspicious granulomatous inflammation.

Among 16 patients with nondiagnostic FNA material, regardless whether acellular (n=6), with scanty cellularity (n=9) or necrotic (n=1), histology found 7 HL, 1 NHL, 2 reactive lymphoid hyperplasia, 2 chronic lymphadenitis, 2 metastases, 1 sinus histiocytosis and 1 granulomatous inflammation.

Discussion

The H&N region is unique because of the proximity of various organs and tissues on a relatively small space. The diversity of H&N masses, from congenital cystic masses, inflammations, primary tumors of the organs from this region to lymphomas and metastatic tumors, requires rapid, safe and as much as possible accurate diagnosis. In our institution, the first diagnostic approach in the diagnosis the H&N masses, in the vast majority of the cases, is FNA cytology.

During a 2-year period, FNA cytology was performed in 494 patients with H&N masses in our department. The most frequent cytological diagnosis was reactive lymphoid hyperplasia, metastatic carcinoma and lymphoma, like in other similar studies [2-4]. Surgical excision or operation was performed in 164 (33.2%) patients, which made it possible to correlate cytological and histological diagnosis. In this group of patients the most frequent cytological diagnoses were metastatic carcinoma, lymphoma and reactive lymphoid hyperplasia. Nondiagnostic cytological material was found in 9.75% of the patients. Flynn et al. in a series of 135 patients reported 5%, Kaur et al. in a series of 123 patients 12.2% and Gupta et al. in a series of 218 patients found 18.8% unsatisfactory material, despite of 2 or 3 repeated samplings [5-7].

In the group of 148 patients in which FNA was adequate, accuracy for malignant lesions was 91.89% and overall concordance in cytologic and final histologic diagnosis was 87.16%. Carrol et al. found an accuracy for malignant lesions of 87% in a series of 78 patients with H&N masses [8]. Our results on sensitivity (91.5%), specificity (92.85%), PPV (97%) and NPV (81.25%) are in concordance with the findings of other authors, who also found slightly higher specificity than sensitivity and lower NPV than PPV [5,7,9]. Also, our results are in concordance with the results of accuracy, sensitivity, specificity, PPV and NPV (93.1, 89.6, 96.5, 96.2 and 90.3%, respectively) found in a systematic review of the published literature and meta-analysis of 30 studies with 3,459 FNA of H&N masses [10].

Although FNA cytology is highly reliable in identifying metastatic carcinoma, 3 metastases were not recognized; 1 lymphoepithelioma and 2 cases of metastases of papillary thyroid carcinoma; this represents a true misdiagnosis.

Lymphoepithelioma is the descriptive diagnosis of an undifferentiated carcinoma which is generally primary nasopharyngeal squamous cell carcinoma of

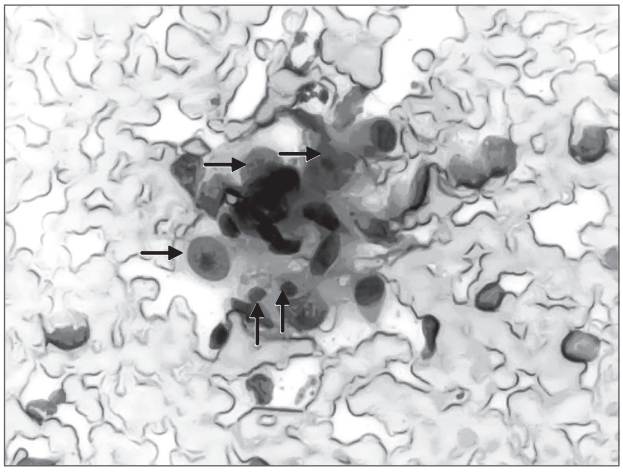

Figure 2. Lymphoepithelioma. Small loose cluster of large vesicular cells with prominent nucleoli on the background of blood (horizontal arrows), rare reactive lymphoid cells and eosinophils (vertical arrows) (MGG ×400).

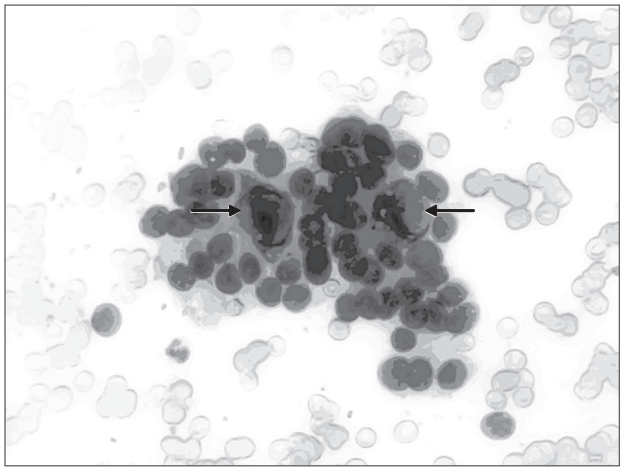

Figure 4. Metastasis of thyroid papillary carcinoma. A papillary cluster of crowded and overlapped cells surrounding globules of colloid (arrows) (MGG ×400).

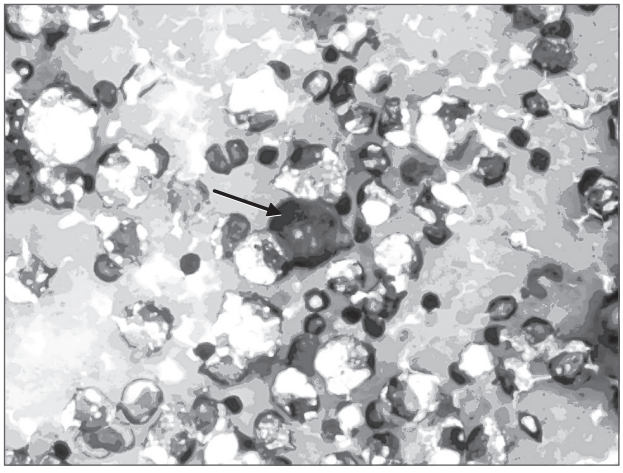

Figure 3. Malignant fibrous histiocytoma. On a background of erythrocytes, there are numerous macrophages, monocytes and lymphocytes, and one megakaryocyte (arrow) (MGG ×400).

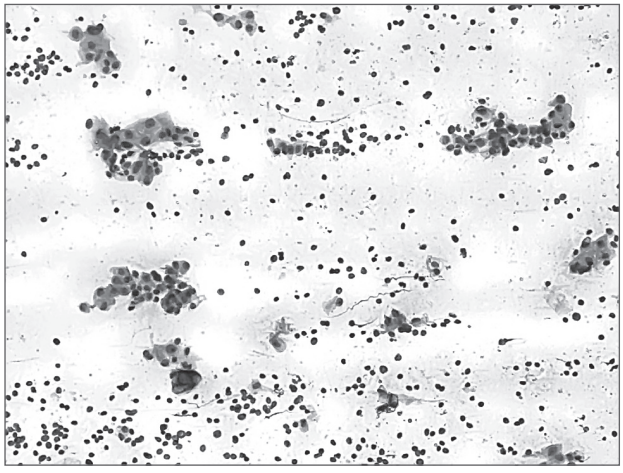

Figure 5. Mucoepidermoid carcinoma. Abundant mucus in a background with small and large sheets of epithelial bland glandular cells (MGG ×100).

poor differentiation that metastasizes to cervical lymph nodes, often as primary clinical presentation (as it was in this case), or it can also be a relatively uncommon malignant tumor of the salivary glands. Review of the aspirate reported as suspicious HL, with final diagnosis of lymphoepithelioma, showed only several small loose clusters of large vesicular cells with prominent nucleoli and rare reactive lymphoid cells with eosinophils. The epithelial cells were mistaken for histiocytes, and because of the presence of eosinophils, a wrong diagnosis of suspicious HL was set. This incorrect diagnosis was a consequence of making conclusion based on scanty diagnostic material.

From this series of H&N masses, thyroid gland was excluded. But, in 4 patients, cells of thyroid gland origin were found in FNA smears from neck masses, and in all 4 cases the cytological diagnosis was wrong. The reason for these misdiagnoses in 2 cases of metastasis of papillary thyroid carcinoma was the lack of enough representative material in one (only the cystic part of the tumor was aspirated with macrophages, scanty colloid and scanty amount of thyroid cells), and wrong interpretation in the other one (a mass was localised submandibularly, and balls of colloid were wrongly interpreted as globullae of stromal material in adenoid-cystic carcinoma). The reason of wrong cytological interpretation of 2 colloid nodular goiters (reported as suspicious carcinoma and suspicious metastasis of thyroid carcinoma) was high cellularity of the aspirated material and low experience in thyroid cytology.

All cytologically diagnosed squamous cell carcinomas and small cell carcinomas were confirmed by histology and there was no any differential diagnostic dilemma about small cell carcinoma - lymphoma. There were 2 misdiagnoses for adenocarcinoma (cytologically reported as adenosquamous and squamous cell carcinoma), but, it is obviously not easy to give the exact type for poorly differentiated carcinomas only on morphology, without special staining.

The accuracy for metastatic disease, which according to the literature reaches 85-96% [11], was 94.5% in our group.

It is well known that cytologic diagnosis of primary lymphoproliferative disorders is one of the most difficult fields in cytology, especially when it is based only on morphology, like we did. Sometimes it is not easy to distinguish between reactive and malignant lymphoid proliferation, as it was in some of our cases. Among the 15 cytologic diagnoses of reactive lymphoid hyperplasia, histology confirmed only 6, while 7 were lymphomas (2 HL and 5 NHL), 1 granulomatous lymphadenitis, and 1 sinus histiocytosis. Review of smears with final diagnosis of HL showed scanty diagnostic material in both smears, with several Hodgkin's-like cells in 1, and 1 suspicious Reed-Sternberg cell in another smear, on a background of rare lymphoid cells, so it was possible to rise suspicion for HL. The diagnostic error in these cases was attributed to inexperience. Among 5 NHL, 3 were follicular lymphomas and the smears from these cases showed a mixed lymphoid pattern which favored a reactive rather than a neoplastic process, and 2 were small lymphocytic lymphomas.

In the case of granulomatous lymphadenitis cytologically reported as reactive lymphoid hyperplasia, FNA showed a mixed lymphoid population with occasional histiocytes consistent with a reactive node, without presence granulomatous component.

Sinus histiocytosis is a very common reaction pattern in lymph nodes draining a distant infection or tumor. The sinuses become dilated and filled with macrophages, few if any of which contain phagocytosed material. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is a rare entity. Histologically, the nodes are characterized by sinuses being grossly dilated from huge numbers of large macrophages with cytoplasm filled with lymphocytes and occasionally other cells, which are not phagocytosed but are just invaginated into the cytoplasm (emperipolesis) [12]. Review of the smear, cytologically diagnosed as reactive lymphoid hyperplasia, with final diagnosis of sinus histiocytosis, showed large histiocytes on a background of reactive lymphoid cells (a lot of lymphocytes, plasma cells) with a group of epithelioid histiocytes. In the cytoplasm of one histiocyte 2 well-preserved lymphocytes were found, which had not been seen before. Should emperipolesis had been found earlier, and attention had been paid on the group of epithelioid histiocytes, it would have been possible to raise suspicion on sinus hyperplasia or Rosai-Dorfman disease. Because the phenotype of epithelioid histiocytes was MAK+/CD68+/S100-, and emperipolesis was not seen, histology excluded Rosai-Dorfman disease in that case.

All 3 cytologically suspicious lymphomas without further classification regarding the type were histologically confirmed as lymphomas, and classified as HL. One suspicious NHL was histologically confirmed, but the final diagnosis for 2 suspicious HL was lymphoepithelioma (aforementioned) and Kikuchi's lymphadenitis.

Kikuchi's lymphadenitis or "necrotizing lymphadenitis without neutrophil polymorphs", is characterized by loose granulomatous nodules in the paracortex, composed of a mixture of macrophages some of which have crescent-shaped nuclei, a typical feature of this condition. Some of the macrophages may be quite blastic, causing concern about lymphoma. Usually the centre of the nodule is necrotic [12]. Although the FNA specimen showed a large admixture of blood, it contained groups of histiocytes with necrotic material and rare cells of lymph node, so, on review, it was seen that there were enough elements to consider necrotizing lymphadenitis, although no crescent macrophages were found.

The diagnostic accuracy for a diagnosis of lymphoma in our series of 52 lymphoid aspirates was 78.8%, sensitivity and specificity were 83.3 and 80%, respectively. Stewart et al. in their series of 277 lymphoid aspirates reached very high accuracy of 97%, with sensitivity and specificity of 91 and 95%, respectively, but their morphological assessment was complemented with ancillary techniques (immunocytochemistry, *in situ* hybridization for immunoglobulin light chain mRNA and polymerase chain reaction) [13].

Special attention was paid to misdiagnoses which were found in 19 patients in total. Most of them were previously mentioned. FP and FN cytological diagnoses for malignancy were seen in 3 (2%) and 9 (6.1%) patients, respectively. In a series of 110 patients with H&N masses Schelkunet al. found 0.5% FN diagnosis, and Gonzales et al. in a series of 172 patients found 1.2% FP and 1.7% FN diagnosis [9,14].

There were 2 misdiagnoses in salivary gland tumor (confusion with mucoepidermoid carcinoma). In one case, the cytological diagnosis was benign salivary gland obstruction, while the final histological diagnosis was mucoepidermoid carcinoma. From the node in the submandibular region 3 ml of haemorrhagic content was aspirated twice; inflammation without necrosis

and without malignant cells was found in the sediment, which led to wrong diagnosis of benign salivary gland obstruction. Although cystic salivary gland aspirates may have broad differential diagnoses (from congenital cysts, benign obstruction, benign or malignant salivary gland lesions, to metastatic tumors), the most frequent differential diagnostic difficulty is between a nonneoplastic duct-obstructing lesion and low-grade mucoepidermoid carcinoma [15].

In the other case, cytological diagnosis was mucoepidermoid carcinoma because there was abundant mucus in the background of the aspirate with small and large sheets of epithelial bland glandular cells, but the final histology was basal cell carcinoma. Review of histology was asked, which confirmed the cytological diagnosis.

Malignant fibrous histiocytoma was misdiagnosed as extramedullary haematopoiesis because of 2 megakaryocytes which were found in the sediment of the cystic aspirate, among numerous macrophages and monocytes. The cytological features of the neoplastic cells are highly variable in malignant fibrous histiocytoma. The neoplastic cells may be spindle to polygonal-shaped, arranged in a dissociate fashion, but no such cells in the sediment of the aspirated material existed, so it was not possible to give correct cytological diagnosis.

In summary, this study of 148 FNA cytology specimens of H&N masses showed an overall accuracy of 91.89% in differentiating benign from malignant conditions, and of 87.16% for the exact type of diagnosis. Review of the misdiagnosed cases showed that the main causes for wrong diagnoses were sampling errors, inexperience, and misinterpretation. In addition, there were also some cases in which it was hardly possible to give correct diagnosis based only on morphology, so wrong diagnosis is almost unavoidable even when the cytologist is experienced in performing and interpreting FNA cytology. Applying ancillary studies to cytological samples would certainly contribute to improved diagnostic accuracy, but this would enhance cost-effectiveness, delay diagnosis and also, it would not always be possible to apply them because of scanty material.

Even with these limitations, FNA cytology is a very useful diagnostic tool, suitable for the first diagnostic line in the management of H&N masses.

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