Leaders

Diagnostic problems in fine needle aspiration cytopathology of the salivary glands

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Introduction

The practice of fine needle aspiration cytopathology (FNAC) of the salivary glands was established between 1964 and 1971 in a series of six papers from the Karolinska Institute, Sweden.¹⁻⁶ Further interest in the technique was initially slow to develop, but by 1987 Layfield *et al*⁷ were able to review 36 papers on the topic and since then, with the general increase in its use, the method has continued to gain in popularity.⁸

FNAC offers many advantages to both clinician and patient. It is safe, economical, and in many instances permits rapid diagnosis with minimal inconvenience or pain. In the salivary glands, where Trucut and incisional diagnostic biopsy have never found favour, FNAC can frequently provide a preoperative diagnosis to guide the surgeon on the degree of urgency necessary for admission, allow planning of the surgical approach and permit informed preoperative discussion with the patient. FNAC can also establish a definitive diagnosis of malignancy in patients who are clinically unsuitable for radical surgery or who have suspected recurrent or metastatic disease. Because of the possibility of sampling error, "negative" cytology is not reliable as a sole means of excluding malignancy, but taken in conjunction with other findings it provides additional reassurance in cases of benign sialadenopathy.

Interpretation of FNAC from the salivary glands is, however, a difficult cytopathological technique with many problems and pitfalls.^{9,10} Although some of these are similar to those encountered in the interpretation of histological material¹¹ and are due to the varied and heterogeneous nature of salivary gland neoplasia, other dilemmas are inherent to FNAC—namely, uncertainty as to the site and tissues actually aspirated, minimal material, and the lack of architectural pattern in smears compared with histological sections.

The interpretation of an aspirate from a mass suspected to be a salivary gland neoplasm must be approached in two stages. First it is necessary to decide if the lesion is indeed of salivary gland origin and not one of the various other entities which can resemble salivary gland disease on clinical examination. Once the salivary gland aetiology of the mass has been established then the pathologist can proceed to the second stage and consider specific salivary gland disorders and arrive at a defini-

tive or differential diagnosis according to the nature of the cellular material. Problems can be encountered during both stages of interpretation and in some instances—for example, aspirates displaying evidence of lymphoproliferation or a squamous cell lesion—it is not possible to distinguish between extrinsic and intrinsic aetiology.

Problems caused by extrinsic disease

Clinical acumen allied to modern imaging techniques contribute much to the assessment of suspected salivary gland disease but findings are sometimes equivocal and lesions of many other origins may be clinically misdiagnosed as sialomegaly and investigated by FNAC (table 1).¹²⁻¹⁸

The most common problem is distinction between enlarged lymph nodes and sialomegaly. Lymph nodes are often enclosed within the parotid gland and it is not possible to differentiate intraparotid lymphadenopathy and true salivary gland enlargement by palpation alone. Similar dilemmas occasionally arise with perisalivary lymph nodes and the submandibular gland.

An aspirate from a hyperplastic lymph node contains lymphocytes, follicle centre cells, and "tingible body" macrophages. If the needle also traverses salivary gland tissue then the resulting mixture of ductal or acinar cells plus cells of the lymphoid series may be difficult to distinguish from salivary gland disease associated with lymphocytosis. In the case of malignant disease, metastatic carcinoma especially of squamous cell or anaplastic type can be impossible to differentiate from primary salivary gland neoplasia as can nodal and extra-nodal non-Hodgkin's lymphomas.

Some of the other lesions—for example, paraganglioma—are rarely encountered, but a branchial cleft cyst in the anterior parotid gland can be confused with cystic salivary gland disease, and a neurilemmoma with a pleomorphic adenoma.^{16,18} Pilomatrixoma seems to be the skin adnexal tumour most

Table 1 Lesions which may mimic sialomegaly

Lymph nodes
Nerve sheath tumours
Branchial cleft cysts
Adnexal and other subcutaneous tumours
Soft tissue lesions
Paraganglioma

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likely to be mistaken clinically for salivary gland disease,¹⁸ and nodular fasciitis the most problematical soft tissue condition.¹⁷ The possibility of cytological misdiagnosis is minimised by experience and continual alertness for the unexpected. It is further reduced if the cytopathologist undertakes the aspiration and thus gains knowledge of the exact anatomical location of the mass.

Problems caused by intrinsic disease

There is perhaps no tissue in the body subject to such a diverse range of neoplastic and non-neoplastic disease as the salivary glands. The classification of salivary gland tumours has progressively evolved and expanded and now includes many heterogeneous and rare lesions.^{19,20} It is therefore not surprising that diagnosis by FNAC is associated with some difficulties. The main interpretative problems associated with intrinsic disorders are given in table 2. However, as indicated earlier, it is sometimes not possible to differentiate between intrinsic and extrinsic disease and where appropriate this is indicated in the subsequent tables of differential diagnoses.

LIPOMATOUS LESIONS

FNAC diagnosis of salivary gland disease depends on the recognition that salivary tissue has been sampled. A percentage of fine needle aspirates, regardless of site, are inadequate for diagnostic purposes as there is no cellular evidence that the suspected lesion has been sampled. Often such specimens contain just streaks of blood mixed with clusters of subcutaneous fat cells. Layfield *et al*²¹ have drawn attention to the possibility of overlooking lipomatous lesions of the parotid gland by incorrectly classifying the aspirates as inadequate. Substantial fat deposition within the parotid gland is rare, but the development of a lipoma or chronic lipomatosis can result in a localised or diffuse swelling which clinically may suggest a Warthin's tumour. FNAC of such glands yields mature adipose cells with almost certainly scant ductal or acinar cellular material. Increased awareness of the possibility of lipomatous lesions will reduce the possibility of an erroneous "non-diagnostic" report by the cytopathologist.

CYSTIC LESIONS

There are very many causes of true or pseudocystic change in the salivary glands in addition to several extrinsic conditions which may be mistaken for sialadenopathy and from which fluid can be aspirated. The main causes are given in table 3.

Table 2 Interpretative problems in FNAC of salivary glands

Lipomatous lesions
Cystic lesions
Lymphoproliferative lesions
Unusual pleomorphic adenomas
Squamous cell lesions
Oncocytic lesions
Rare tumours and tumour-like lesions

Table 3 Differential diagnosis of lesions which may yield "cystic" fluid

Intrinsic:	
<i>Non-neoplastic</i>	
	Obstructive sialadenopathy (retention cyst, mucocoele)
	Salivary duct cyst
	Lymphoepithelial cyst
	Dysgenetic (polycystic) disease
<i>Neoplastic</i>	
	Warthin's tumour
	Pleomorphic adenoma
	Mucoepidermoid carcinoma
	Acinic cell carcinoma
	Cystadenocarcinoma
Extrinsic:	
<i>Non-neoplastic</i>	
	Branchial cleft cyst
<i>Neoplastic</i>	
	Necrotic metastatic carcinoma in intraparotid or perisalivary lymph node

Non-neoplastic disease

Cystic lesions are most commonly associated with obstructive sialadenopathy. A deep-seated tense retention cyst (mucocoele) may lead to clinical suspicion of neoplasia and therefore be a target for FNAC. The fluid is watery or viscous, depending on the nature of the lining epithelium and, if there is no associated inflammation, relatively hypocellular. Secondary infection is not uncommon, however, and then abundant leucocytes, debris, and degenerate epithelial cells are found. The epithelial cell changes in chronic sialadenitis and sialolithiasis can be quite pronounced and include not only nuclear enlargement and hyperchromasia but also squamous or oncocytic metaplasia.

Other forms of non-neoplastic cystic disease are unusual. Dysgenetic cysts occur as part of a rare malformation of the ductal system. Cystic lymphoid hyperplasia is associated with AIDS and a florid lymphocytosis will be found in the fluid.²² Squamous cells and lymphocytes are both present in the contents of a branchial cyst.

Apart from the possibility of worrying nuclear or metaplastic changes associated with chronic obstructive sialadenopathy, there are no pitfalls in the cytological interpretation of fluid aspirated from non-neoplastic cystic disease. Diagnostic problems arise from non-representative sampling of tumours containing cystic areas so that the neoplastic nature of the lesion cannot be appreciated by cytological examination of the aspirated fluid.

Neoplastic disease

Contrary to expectation based on terminology, aspiration of adenoid cystic carcinoma does not yield fluid. A small quantity of thick fluid is, however, almost invariably obtained from a Warthin's tumour and occasionally from a pleomorphic adenoma. Material from a Warthin's tumour generally contains streaks of lymphocytes, amorphous debris, and flat sheets of oncocytes. However, if the latter are sparse, the true diagnosis may not be apparent. An aspirate from a pleomorphic adenoma containing extensive mesenchymal material may be paucicellular and mainly consist of mucomyxomatous material which can be mistaken for the contents of a cyst. Both these are

benign tumours; more serious is failure to sample representative cellular material from a malignant tumour. The low grade subtype of mucoepidermoid carcinoma contains cystic spaces lined by mucus secreting cells. Quite abundant quantities of hypocellular mucus can be aspirated which can lead to a false negative diagnosis of benign cystic disease. Similarly, fluid can sometimes be withdrawn from an acinic carcinoma and the malignant nature of the lesion unappreciated. As previously mentioned, extensive necrosis and liquefaction sometimes occur in lymph nodes replaced by metastatic squamous cells or anaplastic carcinoma. Several millilitres of blood stained fluid can be withdrawn from such nodes. While careful microscopic examination will usually identify malignant cells in this type of specimen, these may not be obvious, particularly in well differentiated squamous cell carcinoma. As such nodes are often labelled "cyst fluid" by the aspirator a misdiagnosis of branchial or other non-neoplastic cyst is a potential pitfall.

The experienced cytopathologist is aware of these problems and guards against error by giving a cautious opinion on cyst fluid, particularly if it is bloodstained or contains much cellular debris. It is a safety rule in FNAC practice, and this applies not only to the salivary glands, that after aspiration of a cyst the site of the lesion is carefully re-examined and any residual palpable abnormality is re-needed. If this is done representative neoplastic cells will be obtained from the more solid tumour adjacent to the cystic area and an erroneous diagnosis avoided.

LESIONS ASSOCIATED WITH LYMPHOPROLIFERATION

Conditions which may result in a "lymphoid cell rich" aspirate are shown in table 4. Numerous lymphocytes are sometimes seen in association with chronic sialadenitis and are the rule in granulomatous sialadenitis. Evidence of salivary gland disease is present in about 6% of cases of sarcoidosis.²³ At FNAC, multinucleated giant cells and clusters of epithelioid cells are seen in addition to lymphoid cells.²⁴ Myoepithelial sialadenitis (MESA) is the most likely form of lymphoepithelial disease to present to the cyto-

pathologist. FNAC preparations contain lymphocytes, follicle centre cells, plasma cells and histiocytes. Clusters of myoepithelial cells, if present, are a helpful diagnostic pointer, but they are not always evident and then distinction from other causes of lymphoproliferation is difficult. If insufficient material is available for immunocytochemistry differentiation from low grade non-Hodgkin's lymphoma can be taxing especially as this may supervene on benign lymphoepithelial disease.²⁵

Various neoplasms, most obviously Warthin's tumour, but also on occasions pleomorphic adenoma, mucoepidermoid carcinoma, and acinic cell carcinoma, are associated with lymphocytosis. Careful scrutiny of the slides for evidence of neoplastic cells will usually avoid mistakes. Diagnosis of high grade non-Hodgkin's lymphoma is generally straightforward on FNAC material. Without immunocytochemistry, distinction between florid lymphoid hyperplasia and low grade lymphoma is not easy to accomplish. In neither type of disease can nodal and extra-nodal lymphoma be successfully separated. The cytological diagnosis of Hodgkin's disease depends on the recognition of Reed-Sternberg cells and therefore directly depends on the number within any particular tumour deposit.

UNUSUAL PLEOMORPHIC ADENOMAS

In almost all cases cytological diagnosis of pleomorphic adenoma is straightforward and highly accurate.^{7 10 26-32} Aspirates contain epithelial cells intermingled with loose clusters of mesenchymal cells and fibrillary mucomyxomatous background substance.⁸ Problems in interpretation can arise for two reasons: the predominance of one element leading to the apparent absence of the other components; or the presence of atypical cytomorphological features.

If the epithelial cells dominate the specimen the tumour may be mistaken for a monomorphic adenoma rather than a mixed tumour. If the mesenchymal elements are overabundant and epithelial cells sparse then the lesion may be erroneously termed a cyst. More serious, however, is false suspicion of malignancy.^{3 7} Occasional pleomorphic adenomas are densely cellular and display marked cytological "atypia". This is reflected in FNAC specimens in which the epithelial cells show loss of cohesion, anisonucleosis, and nuclear hyperchromia.

It is of considerable practical importance not to "overcall" these changes. On resection such tumours may indeed contain areas of in situ carcinoma but this does not alter the prognosis and management is comparable with that required for "usual-type" pleomorphic adenomas. Frank carcinoma ex-pleomorphic adenoma, necessitating radical treatment, is an aggressive, poorly differentiated lesion. Aspirates almost invariably contain numerous anaplastic malignant cells without any cytological features of residual pleomorphic adenoma.⁸ Therefore, if evidence of mesenchymal material is recognisable in an FNAC, even if the epithelial cells

Table 4 Differential diagnosis of "lymphoid cell rich" aspirates

Intrinsic:	
<i>Non-neoplastic</i>	
	Chronic sialadenitis
	Granulomatous sialadenitis
	Lymphoepithelial disease
	Myoepithelial sialadenitis (MESA)
	Sjögren's syndrome
	Cystic lymphoepithelial hyperplasia of AIDS
<i>Neoplastic</i>	
	Warthin's tumour
	Mucoepidermoid carcinoma
	Acinic cell carcinoma
	Malignant lymphoma
Extrinsic:	
<i>Non-neoplastic</i>	
	Benign lymphadenopathy of intra or perisalivary lymph nodes
<i>Neoplastic</i>	
	Malignant lymphoma of nodal origin

do display worrying features, a cautious report is indicated. The other important problem is that a few pleomorphic adenomas contain adenoid cystic-like areas. Globules of basement membrane material surrounded by small epithelial cells, similar to those seen in true adenoid cystic carcinoma,⁸ can then be present in FNAC preparations. If the globules are few and other features of pleomorphic adenoma are present, false suspicion of malignancy should not occur but the distinction can be as difficult as it can on a small histological biopsy specimen. Close clinical correlation is helpful as a history of pain or nerve dysfunction usually accompanies adenoid cystic carcinoma but is absent in adenoma. Nevertheless, if there is any doubt, definitive diagnosis should not rest on FNAC alone and frozen section is indicated. Extensive squamous metaplasia in pleomorphic adenomas may raise a suspicion of squamous cell neoplasia but careful examination of the characteristics of the squamous cells will solve this problem. It should also be noted that very occasionally mucin is produced by pleomorphic adenomas and this is reflected in the cytological findings.³³

SQUAMOUS CELL LESIONS

The list of differential diagnoses to be considered when squamous cells are found in an FNAC from a suspected salivary gland mass is given in table 5. Among malignant lesions in particular it may not be possible to distinguish intrinsic salivary gland disease from an extrinsic disorder.

Squamous cells arising from foci of benign squamous metaplasia are sometimes seen in aspirates from chronic sialadenitis but seldom are of troublesome morphology. More worrying is the bizarre metaplastic change which may occur as the result of irradiation or in necrotising sialometaplasia.³⁴ The latter is rare and virtually confined to the palate but is an acknowledged potential source of a histological false positive report of malignancy¹¹ and must therefore be considered a similar problem in cytological specimens. Post-radiation sialadenitis is a less uncommon difficulty and, although knowledge of the history of irradiation is helpful as the treatment will have been administered for neoplastic disease in the first

place, the bizarre squamous cell changes may still pose a diagnostic dilemma. Florid squamous metaplasia is sometimes seen in benign neoplasms, notably Warthin's tumours and pleomorphic adenoma. The possibility of a misdiagnosis of squamous cell carcinoma was noted by Seifert *et al* in their review of the histology of Warthin's tumour³⁵ and at least one case is documented in which a false positive FNAC diagnosis occurred.³⁶

All the above raise the possibility of the misdiagnosis of benign squamous metaplasia for carcinoma. However, problems also arise with FNAC specimens which contain undoubted malignant squamous cells. These may arise from a primary squamous cell carcinoma, metastatic (nodal) squamous cell carcinoma, or represent a component of mucoepidermoid or adenosquamous carcinoma of the salivary gland. There are no cytological features which can reliably differentiate primary and metastatic squamous cell carcinoma and history is therefore of paramount importance. Pure squamous cell carcinoma of primary salivary gland origin is, however, rare. Recognition and typing of mucoepidermoid carcinoma is a difficult exercise on FNAC. The low grade subtype may be predominantly cystic and mistaken for a benign retention cyst or Warthin's tumour, and the high grade subtype can be misdiagnosed as a squamous cell carcinoma. The mucus secreting component is sometimes extremely sparse in the latter and in some examples of high grade mucoepidermoid carcinoma may not be identifiable at all in FNAC preparations. It is therefore not feasible in such instances to distinguish between this tumour and pure primary or secondary squamous cell carcinoma. The recognition of intermediate cells and groups of multilayered overlapping cells among the squamous cells are the most helpful cytological indicators of high grade mucoepidermoid carcinoma if mucus secreting cells are absent.³⁷ Adenosquamous carcinoma of the salivary glands is a very rare tumour but must also be considered in the differential diagnosis of squamous cell lesions. The potential pitfall of confusion between the contents of a branchial cleft cyst and an aspirate from a necrotic squamous cell carcinoma has already been mentioned.

ONCOCYTIC LESIONS

Many non-neoplastic and neoplastic salivary gland lesions can display oncocytic features. The main entities are shown in table 6. Focal oncocytosis is common in the elderly and is

Table 5 Differential diagnosis of squamous cell lesions

<i>Intrinsic:</i>	
<i>Benign</i>	
	Squamous metaplasia
	Chronic sialadenitis
	Post-radiation sialadenitis
	Necrotising sialometaplasia
<i>Tumour metaplasia</i>	
	Pleomorphic adenoma
	Warthin's tumour
<i>Malignant</i>	
	Squamous cell carcinoma
	Mucoepidermoid carcinoma
	Adenosquamous carcinoma
<i>Extrinsic:</i>	
<i>Benign</i>	
	Branchial cleft cyst
<i>Malignant</i>	
	Metastatic squamous cell carcinoma in intraparotid or perisalivary lymph node

Table 6 Differential diagnosis of oncocytic lesions

<i>Benign:</i>	
	Focal and diffuse oncocytosis
	Nodular oncocytic hyperplasia
	Oncocytoma
	Warthin's tumour
	Oncocytic tumour metaplasia
	Pleomorphic adenoma
	Other
<i>Malignant:</i>	
	Oncocytic carcinoma
	Mucoepidermoid carcinoma

often seen in association with chronic sialadenitis. The most usual differential diagnosis is Warthin's tumour in which the associated lymphocytosis is helpful. Florid diffuse oncocytosis and nodular oncocytic hyperplasia are very rare lesions which may clinically mimic neoplastic disease. Distinction from the rare oncocytoma is probably not feasible by FNAC. Oncocytic metaplasia in other benign tumours, such as pleomorphic adenoma, is more common than oncocytoma. In the solitary example I have examined, of FNAC from the rare oncocytic carcinoma, the cells displayed unmistakable stigmata of malignancy with residual oncocytic characteristics remaining in the better differentiated areas. The main differential diagnosis is mucoepidermoid carcinoma with oncocytic changes but again this is a rare type of tumour.

RARE TUMOURS AND TUMOUR-LIKE CONDITIONS

Numerous rare tumours^{19 20} and tumour-like conditions¹⁹ occur in the salivary glands. The classification of adenomas has recently been reviewed and several new types of carcinoma recognised.^{19 20} Cytological experience of uncommon entities is of necessity extremely limited, although as the use of FNAC becomes more widespread this will increase.

Tumour-like conditions

Several different lesions are now listed under this heading in the WHO classification.¹⁹ Oncocytosis, sialometaplasia, cysts and lymphoepithelial disease have already been mentioned. Sialadenosis can be diagnosed from FNAC by consideration of the morphology of the abundant acinar cells, supplemented if necessary by morphometry.³⁸ This condition is usually bilateral which is a helpful indicator of non-neoplastic disease. If it is unilateral well differentiated acinic cell carcinoma may be falsely suspected. The one example I have seen of FNAC from a case of sclerosing sialadenitis of the submandibular gland contained ductal cells with nuclei which displayed a worrying degree of hyperchromasia. Aufdemorte *et al*³⁹ have drawn attention to the differential diagnostic problem which may be caused by adenomatoid hyperplasia.

Adenomas

Apart from pleomorphic adenoma and Warthin's tumour, descriptions of cytomorphology are currently sparse. Of particular importance is the report by Stanley *et al*⁴⁰ in which he states that it does not seem feasible to distinguish between basal cell adenoma and adenoid cystic carcinoma. Two recent cases that I examined confirm this opinion. Other authors have also commented on diagnostic difficulties arising from uncommon adenomas and the possibility of false suspicion of malignancy.⁴¹⁻⁴³

Carcinomas

Descriptions of FNAC from terminal duct carcinoma,⁴⁴ oncocytoid carcinoma,⁴⁵ small

cell carcinoma^{46 47} and epithelial myoepithelial carcinoma⁴⁸⁻⁵⁰ are available. On review, in most instances, the cytological features were considered sufficiently characteristic to indicate the true tumour type, but the correct classification was seldom achieved on initial examination due to unfamiliarity with the cytomorphology of the uncommon neoplasm.

Discussion

Overall, use of FNAC can obviate the need for surgical intervention in one third of patients²⁷ and provide helpful preoperative diagnostic information in most of those undergoing surgery.

Sensitivity of FNAC in series with good histological and clinical correlation ranges from 81% to 100%, and specificity from 94% to 100%.^{7 10 18 26-32 51-53} When considered from the viewpoint of precise diagnosis—that is, indication of the disease process in non-neoplastic lesions and the exact classification of tumours—a definitive answer can be provided in 61% to 80% of cases.^{29 30} The largest study among recent publications looked at the results of 582 aspirates.⁵⁴ There were 21 discrepant cases, in 10 of which the specimens were essentially inadequate. Among the remaining 11, there was only one potentially important misdiagnosis (a case of chronic sialadenitis mistaken for pleomorphic adenoma); the other examples were false negative diagnoses or misclassifications between benign neoplasms.

The results of FNAC are very comparable with those of frozen section. Auclair *et al*⁵⁵ reviewed frozen sections of the salivary glands. Overall accuracy calculated from 21 series was 96.2%, excluding deferred diagnoses. If only malignant tumours are included the rates with and without deferred diagnoses are 77.1% and 85.7%, respectively. Several papers^{7 32 56} have directly compared the results of FNAC and frozen section from the same lesions and in each the accuracy of FNAC was slightly higher. The convenient preoperative timing, ease of specimen collection, freedom from complications and ready repeatability of FNAC encourage clinical enthusiasm for the technique. Nevertheless, it is prudent to adopt a cautious approach and to consider FNAC and frozen section as complementary investigations. No assessment of invasion or information about the planes of resection is possible from FNAC. Also, because of the problems of sampling and the cytological similarity of some disparate conditions,⁵⁴ there will always be occasions where it is safer to limit the FNAC report to a differential diagnosis and advise frozen section. A conservative attitude to FNAC of the salivary glands will still provide considerable safe diagnostic information to the benefit of both patient and clinician: while most common benign and malignant lesions can be accurately and precisely diagnosed, the not inconsiderable interpretative problems should not be underestimated.

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