Review article

Fine needle aspiration cytology

JV LEVER,* PA TROTT,† AJ WEBB,‡

*From the *Royal United Hospital, Bath, the †Royal Marsden Hospital, London, and ‡Bristol Royal Infirmary, Bristol*

SUMMARY Fine needle aspiration cytology is an inexpensive, atraumatic technique for the diagnosis of disease sites. This paper describes the technique and illustrates how it may be applied to the management of tumours throughout the body. The limitations of the method, the dangers of false positive reports, and the inevitability of false negative diagnoses are emphasised. In a clinical context the method has much to offer by saving patients from inappropriate operations and investigations and allowing surgeons to plan quickly and more rationally. It is an economically valuable technique and deserves greater recognition.

Fine needle aspiration cytology is a simple, inexpensive method for obtaining a tissue diagnosis of subcutaneous and other tumours. The method is used most commonly for the preoperative assessment of breast lumps, but it is also applicable to lymph nodes, thyroid and other lesions in the neck, and, with the aid of a special needle, the prostate. Modern imaging techniques enable the method to be extended to virtually any part of the body.^{1,2}

The technique was introduced in the 1930s by Martin and Ellis³ and Stewart⁴ in the United States, but it never became widespread. Since the 1950s it has been used extensively in Scandinavia^{5,6} and in Holland.⁷ Over the past few years its practice has spread in the United Kingdom.⁸⁻¹¹ The growing popularity of the subject is mirrored by the number of recent books on the topic.^{1,2,10,11} The most obvious advantages of fine needle aspiration cytology over surgical and large needle biopsy (Tru-cut or drill) are that it is quicker to report and perform, less painful, less technically demanding, and easily repeatable. In short, it is far more convenient and may be set up in any clinical situation.

In an ideal setting, fine needle aspiration is part of a clinical sequence in which the doctor examines the patient, performs the aspirate, reads the smear, discusses the cytological diagnosis with colleagues as appropriate, and delivers the report or repeats the whole procedure. In this manner the most accurate

results are achieved. This is standard practice in Scandinavia,¹² selected centres in Europe, and the United States. In other centres it is more likely that clinicians will perform the biopsy and submit the smears to a cytologist for interpretation. Inevitably this style produces a higher proportion of unsatisfactory smears and a lower cytological accuracy.

The philosophy of this form of biopsy and its relation to medical practice outside Scandinavia have been discussed by Fox.¹² Criticisms have been directed towards the tendency to report accuracy rates and failure to identify the applicability of aspiration cytology in clinical practice.¹³

In this paper we review the technique and interpretation of fine needle aspiration cytology and indicate the contribution it can make towards the clinical management of patients.

Material and methods

There are many descriptions of the procedure of fine needle aspiration,⁵⁻⁷ and yet reports of unsatisfactory smears abound.^{14,15} Certain details require emphasis. Local anaesthetic is rarely required for comfort; if used it may alter the palpatory findings and foil the precision of needling. Despite statements to the contrary, a 20 ml plastic disposable syringe is the most satisfactory size coupled with a 21, 23, or 25 gauge needle (Fig. 1).

After the skin has been cleaned with antiseptic,

the tumour is held firmly with one hand and the needle is inserted directly into it. The plunger of the syringe is pulled back, thus exerting suction. This is maintained with the thumb, and the needle is moved through the tumour three or four times in different directions. Still with the needle in the tumour, suction is slowly released. The needle is then removed from the tumour and the syringe from the needle. The syringe is then filled with a little air, reconnected to the needle, and the contents of the needle blown on to one or more clean dry slides, which are rapidly air dried. The constant application of suction while the needle traverses the mass is critical and failure to ensure this probably accounts for many unsatisfactory smears. Syringe pistols attract many adherents,^{9,16} but a braced thumb technique⁸ is equally effective, although the skill requires a little practise (Fig. 1).

The same method may be applied to palpable abdominal masses; no harm is done by passing fine needles through the abdominal viscera. These principles are also applied to lesions outlined by imaging techniques such as radiography and ultrasound.¹ Under these circumstances longer needles are required and asepsis is important. It is helpful to have sterilised microscope slides available so that the needle may be used again if the first attempt at aspiration failed and the needle touched the slide.

The slides are stained by the Romanowski method. Ideally, the dried smears should be fixed in methanol for 5 min and stained with Giemsa or May-Grunwald Giemsa without delay. However, another convenient aspect of fine needle aspiration

cytology is that unfixed smears may be kept in a slide case for up to seven days without detriment before processing.

The use of Romanowski stains is preferred because it is not possible to stain air dried smears satisfactorily with haematoxylin. The alternative of wet fixation is less practicable as the smears dry too quickly. Some cytologists do prefer wet fixation and Papanicolaou staining. Romanowski staining is superior for lymphoid smears and matches the haematological appearances. In other fields the increased cytoplasmic detail is worthwhile, as is enhancement of the smear background.

The clinical application, cytopathology, and the possible pitfalls of needle aspiration depend on the site under consideration. These are considered in order.

BREASTS

Table 1 shows how fine needle aspiration is applied to the clinical management of breast disease. The

Table 1 *Cytology and breast disease*

Clinical	Findings	Action
Cysts	Acellular granular debris	Saves admission
	Cellular fluid Malignant cells present	Follow up or biopsy Urgent admission and frozen section
Benign lump	Benign cells	Routine lumpectomy
	Doubtful cells Malignant cells	Frozen section Urgent admission and frozen section
Malignant lump	Benign	Repeat F.N. or frozen section
	Malignant	Saves frozen section

Fig. 1 Fine needle aspiration of thyroid using a disposable 20 ml syringe and number 1 (21 gauge) needle with skin cleaning swab. This illustrates constant suction by the braced thumb technique.

*Fine needle aspiration cytology*Table 2 *Costs and benefits of breast cytology*

	<i>Cost</i>	<i>Benefit</i>
Patient	Pin prick	Saves hospital admission Saves preliminary biopsy Saves frozen section Knows operation beforehand
Surgeon	Time	Time—saves frozen section Allows rational planning of operating lists Avoids unnecessary admissions
Laboratory	Time	Saves interruption in routine Adds variety and interest
Hospital	Syringe Needle Medi-swab Slides Stain	Saves admissions Saves frozen section Saves preliminary biopsies Saves money

most important emphasis is that mastectomy or whatever is not performed on the results of cytology alone; the cytological diagnosis must be supported by clinical and often mammographic findings.

Table 2 illustrates the cost savings and benefits of aspiration cytology to all concerned with the treatment of breast disease. The feel of the needle as it traverses a breast lump often contributes to the diagnosis. A needle can be felt to puncture a cyst; there is a characteristic gritty texture as one enters most carcinomas; and dense fibrous dysplasia feels firm and seems to grip the needle.

The cytology of breast cyst fluids presents few problems provided one remembers how bizarre some degenerate apocrine cells can appear. Unless breast cyst fluid is blood stained or a mass persists after aspiration, however, there is no need to examine breast cyst fluid smears.¹⁷

Fig. 2 Fine needle aspiration from breast showing well defined acini. Giemsa $\times 360$.

Fig. 3 Histology from the same case as illustrated in Fig. 2. Haematoxylin and eosin $\times 360$.

Fig. 4 Fibroadenoma of breast showing prominent nucleoli and open chromatin of the epithelial cells (centre) but below right is a characteristic sentinel nucleus. Giemsa $\times 900$.

Fig. 5 *Well differentiated carcinoma of the breast. Single isolated cell has a nucleus identical to those in the clumps and must not be confused with a sentinel nucleus. Giemsa $\times$ 900.*

Fibroadenomas of the breast are readily diagnosed cytologically. Characteristically, they yield cellular smears rich in large tight sheets of benign epithelial cells admixed with scattered sentinel nuclei. During aspiration epithelial cells are separated intact in large sheets, whereas only the nuclei of connective tissue cells are aspirated.⁶ The naked sentinel nuclei in aspirates of fibroadenomas and dysplasia are most probably from myoepithelial cells or outer layer of ductal epithelium. Other benign breast lesions may yield very few cells, so that any cellular breast aspirate is an indication of the need for surgical excision.

Breast carcinomas usually provide cellular smears. Because of the loss of adhesion of malignant cells the smears from breast carcinomas are rich in small clumps with scattered individual malignant cells and malignant nuclei. The malignant cells show variation in size, shape, and staining and there is usually a high nuclear to cytoplasmic ratio.

Cytological architecture may be present in some smears and a resemblance to the histological pattern is discernible. The pattern of infiltration is lost in cytological smears, and so one must pay more atten-

tion to the nucleocytoplasmic features. Whereas in formalin fixed histology and wet fixed cytology the chromatin of malignant cells is clumped, definitive, and irregular, in air dried smears of aspiration cytology the chromatin is more bland. Chromatin features clearly separate benign from malignant nuclei. The number of nucleoli is often increased and those present are larger and more irregular than those in benign cells. Many other features contribute to the diagnosis of malignancy.⁶ Although much of the structure is lost in cytology, the occasional preservation of acini (Figs. 2 and 3) and scattered intact trabeculae of cells correlate well with infiltrative features seen histologically.

The prime purpose of aspiration cytology of the breast is to diagnose malignancy, but there is often a striking resemblance between the cytology and the subsequent histology and the smears may be more informative. The mixture of undifferentiated carcinoma cells with numerous lymphoid cells may lead to a provisional diagnosis of medullary carcinoma. The presence of abundant blue staining mucus suggests that the tumour in question is a colloid carcinoma. Cytological preparations are more likely to be misinterpreted as malignant than histology slides.¹⁸ For this reason it is essential to have a comprehensive learning series of case material before embarking on the responsibility of a cytology report being included in clinical management. This may readily be obtained from material submitted for frozen section.¹⁹

Although fibroadenomas are generally correctly diagnosed, there are occasions when the epithelial cells are larger and are arranged in smaller groups, and so they may be confused with malignant cells (Fig. 4). Nevertheless, the benign nature of these lesions should be realised if extra attention is paid to the scattered sentinel nuclei. The presence of these oval nuclei with lunar geographic chromatin and which are often arranged in pairs precludes the firm diagnosis of malignancy.

The pattern of small groups of hyperplastic cells with scattered naked nuclei characteristic of a fibroadenoma must be differentiated from the similar pattern of some breast carcinomas which consists of small groups of malignant cells with scattered malignant nuclei (Fig. 5).

The subacute inflammation of duct ectasia may give rise to occasional bizarre cells. Such cells are usually sparse, however, and the accompanying inflammation with multinucleated epithelioid giant cells and a characteristic blue granular background should point one to the correct diagnosis. In the presence of such features a diagnosis of malignancy should only be made if there is an overwhelming number of obviously malignant cells.

Fine needle aspiration cytology

Fig. 6 *Fine needle aspiration from a lymph node showing groups of epithelioid cells. Giemsa $\times 360$.*

Fig. 7 *Amorphous debris, characteristic of caseation. Giemsa $\times 360$.*

LYMPH NODES

The discovery and speedy diagnosis of enlarged lymph nodes is of greatest clinical importance.¹¹ In clinical disciplines as diverse as rheumatology, paediatrics, and urology, problems abound and clinical evaluation by palpation is often misleading. Fine needle aspiration is of great value in reducing delay in diagnosis, allaying anxiety, and indicating the pattern of investigation.²⁰ There is rarely a need to excise nodes affected by secondary carcinoma unless block dissection is appropriate. Alternatively, reactive nodes and specific infections (tuberculosis and cat scratch disease) may be correctly investigated and treated or, if indicated, subjected to periodic observation. Many reactive nodes, especially in children, will resolve spontaneously.

The diagnosis of Hodgkin's disease by fine needle aspiration will direct investigation and may avoid the risk from ill judged surgical biopsy.²¹ Sometimes one surgical procedure may be avoided, with the definitive and essential histological material being taken at the time of staging laparotomy. The progress of the disease after treatment may be conveniently monitored by aspiration cytology without resort to surgical excision.

For non-Hodgkin's lymphomas the gain is twofold. In advanced cases surgical biopsy may be avoided altogether. Otherwise the diagnosis may be

made quickly and inappropriate procedures avoided.

Imprint cytological smears from each node biopsy will help histology to clarify what is often a perplexing pathological diagnosis.²²⁻²⁴

Aspirates from lymph nodes are usually very cellular, and their interpretation varies from a clear diagnosis to a firm request for immediate histology. Among the diagnostic aspirates is pus, often with bacteria. Epithelioid cells are readily recognised (Fig. 6) together with caseous material (Fig. 7).

Branchial cysts are characterised by the amount of pus like fluid aspirated and the mature squamous cells present therein interspersed with cholesterol crystals. Secondary carcinoma is recognised by the population of malignant cells contrasting with lymphoid elements. Benign reactive lymph nodes are usually diagnosed by the wide range of lymphoid cells present, from the small mature lymphocytes to large centroblasts (Fig. 8). Non-Hodgkin's lymphomas, while difficult, may be recognised by abnormal lymphoid cells with a tendency to monomorphism (Fig. 9). Hodgkin's disease is suspected by the presence of Reed-Sternberg cells (Fig. 10), although these may be difficult to find in the lymphocyte predominant type. In most cases Hodgkin's disease presents little cytological difficulty. Nevertheless, a smear rich in lymphoid cells is never

Fig. 8 A reactive lymph node with all types of lymphoid cells present. A histiocyte containing nuclear debris is well seen towards the bottom right. Giemsa $\times 360$.

Fig. 9 Non-Hodgkin's lymphoma showing a monomorphic picture. Giemsa $\times 900$.

easy to diagnose. The large centroblasts of reactive hyperplasia may be mistaken for Reed-Sternberg cells. An inactive lymph node may give an uncomfortably uniform picture, and therefore whenever a diagnosis of malignant lymphoma is suspected cytologically, histological confirmation is usually sought.

A danger of under diagnosis arises with some aspirates from metastatic squamous carcinoma, which may be remarkably fluid, degenerate, and contain many polymorphonuclear leucocytes, so resembling pus. The value of aspiration cytology lies in its early direction of appropriate investigations. It is quite usual for lymphoid cytological smears to play an important and sometimes critical part in problem lymphadenopathy.

SALIVARY GLANDS

Clinical assessment and palpation of salivary swellings are known to be imprecise.^{11 25 26} It is very helpful for both the surgeon and the patient to know before the operation if the tumour is benign so that the facial nerve can be preserved. If the lesion is malignant and requires wider excision then perhaps sacrifice of some branches of the facial nerve will be obligatory.

It is in salivary gland aspirates that the appearances correlate best with histological patterns (Figs. 11 and 12). With practice, the common types of salivary tumour are readily recognised.^{27 28} In contrast to other sites, the mucin of salivary tumours

stains red instead of blue with Romanowski stains. In the pleomorphic adenoma fibrillary mucin surrounds scattered uniform cells (Fig. 12). In the adenoidcystic carcinoma solid masses of mucus are surrounded by rather bland cells. Acinic, mucoepidermoid, and undifferentiated salivary carcinoma bear distinct features.

THYROID GLAND

The sensible management of goitres is complicated by two major difficulties. Firstly, although easily assessable to palpation, clinical examination is limited in its accuracy.¹¹ About 60% of thyroid cancers present as benign lesions and seemingly solitary nodules are found at operation to be part of a multinodular goitre. Also, 20% of Hashimoto's disease may escape clinical detection,²⁸ especially when the goitre is unilateral and the disease develops in a pre-existing nodular gland. Such cases may closely simulate malignancy. In addition, standard thyroid investigations including ultrasound and scintiscanning are not precise enough to indicate a firm preoperative diagnosis^{30 31} or differentiate benign from malignant nodules.

Hashimoto's disease is readily recognised by the presence of a wide variety of lymphoid cells admixed with Askanazy cells with bizarre nuclei and abundant blue cytoplasm (Fig. 13). Goitres may be recognised by the presence of blue colloid in which lie pigment laden macrophages and occasional intact follicles. Anaplastic carcinomas and malignant lymphomas may be recognised readily. Papillary carcinoma may often be recognised by the presence of numerous intact papillary groups in the smears together with distinctive nuclear features. Follicular carcinoma is difficult to recognise cytologically so one must have a high index of suspicion and report follicular neoplasm only. The cytological assessment of follicular neoplasm awaits complete evaluation. A cellular thyroid aspirate that is not obviously Hashimoto's disease or a nodular goitre is an indication for surgery. Hence, the six so called false positive reports of Suen and Quenville³² are more an indication of sound clinical practice.

The only real false positives in thyroid aspirates are the misinterpretation of Askanazy cells for malignant cells.³³

PROSTATE GLAND

Fine needle aspiration of the prostate is a simple outpatient procedure that is often only a relevant investigation in an elderly infirm man with clinical carcinoma of the prostate.³⁴

Prostatic aspirates are usually cellular. Benign smears are rich in large sheets of regular epithelial cells. Malignant aspirates, if from poorly differenti-

Fig. 10 *Nodular sclerosing Hodgkin's disease illustrating Reed-Sternberg cells. Giemsa $\times 360$.*

Fig. 11 *Pleomorphic salivary adenoma with regular myoepithelial cells entrapped in mucin. Giemsa $\times 360$.*

Fig. 12 *Warthin's tumour of the parotid showing a mixture of epithelial cells and lymphoid cells. Giemsa $\times 360$.*

Fig. 13 Hashimoto's disease of the thyroid with Askanazy cells scattered among lymphoid cells. Giemsa $\times 360$.

ated tumours, are rich in scattered malignant cells. Well differentiated carcinoma cells may be arranged in sheets, but the sheets are smaller and the cells present have less cytoplasm and show some nuclear pleomorphism. Benign conditions, such as granulomatous prostatitis and acute inflammation, are readily recognised but unwisely submitted for aspiration.

Seminal vesicle cells in prostatic aspirates may

Fig. 14 Seminal vesicle cells. Although pleomorphic, the presence of cytoplasmic granules alerts one to the true nature of these cells. Giemsa $\times 360$.

Fig. 15 Seminoma of testis showing malignant cells and the characteristic tiger substance background. Giemsa $\times 360$.

appear pleomorphic and malignant, but the presence of granules in the cytoplasm should alert one to their true nature^{35 36} (Fig. 14).

TESTIS

This is a controversial field for cytological diagnosis. Fine needle aspiration of the testis does enable one to distinguish between inflammation and neoplastic lesions preoperatively, and often the tumour can be classified. Many seminomas have a characteristic "tiger substance" background (Fig. 15), enabling even metastases to be identified as from primary seminoma.⁶

The germinal epithelium of healthy testis appears cytologically disconcerting; usually the presence of spermatozoa alerts one to this pitfall but if there is a maturation arrest a false positive diagnosis is a strong possibility.

LUNGS^{1 2 11 37}

Lung lesions are readily accessible to a fine needle so long as there is a skilled radiologist with the appropriate directing equipment.

The common types of lung carcinoma and secon-

dary tumours can be readily recognised cytologically as malignant and be differentiated from inflammatory lesions. The type of malignancy, however, may be difficult to discern on cytology alone.¹¹

Some carcinomas, particularly of squamous type, undergo central cavitation. It is therefore essential in cavitating lesions to aspirate the wall of the cavity.

Even aspirates from benign lung lesions may be very cellular and are often rich in alveolar macrophages, which should not be mistaken for carcinoma cells. A simple pneumothorax is a common complication of thoracic fine needle aspiration; it occurs in up to 35% of cases, and tension pneumothorax has been described. It is therefore advisable that patients undergoing this procedure are nursed on a chest unit and chest radiographs are taken immediately after the aspirate and after an appropriate interval.¹ Haemoptysis is not uncommon after the biopsy, and although this is usually of no clinical importance, the patient should be warned.

ABDOMEN

Palpable lesions in the abdomen may be aspirated and the finding of malignant cells may well obviate the need for hospital admission and prolonged investigation. Inpalpable lesions found by ultrasound or computed tomography may be aspirated preferably by a radiologist under directed control. This is particularly useful for suspected liver metastases identified by ultrasound.³⁸ Hepatocytes have a characteristic appearance which is different from secondary carcinoma.¹ The pancreas is easily reached with ultrasound control and there is no difficulty recognising poorly differentiated carcinomas. Care is required as pancreatic aspirates may be very cellular, even when benign, and chronic pancreatitis may lead to cellular atypia. This is an important diagnostic pitfall.

Renal lesions may be readily aspirated. Renal carcinoma cells have a characteristic appearance with regular nuclei and abundant vacuolated cytoplasm. Care must be taken to differentiate these cells from foamy macrophages.

Discussion

As a clinical procedure fine needle aspiration is inexpensive, requires simple equipment, and is not time consuming. It is suitable for other disease sites not included in this paper.¹ When performed by a clinician in an outpatient clinic or at the bedside it is best regarded as an extension of the physical examination. On this score, the expectations of the clinician and the potential of cytology vary with the site aspirated. In the case of breast aspirates, up to 85%

of carcinomas should be firmly diagnosed cytologically. Most fibroadenomas will be similarly correctly identified. The problem arises with other benign breast diseases, particularly those characterised by fibrosis when few cells are aspirated. A negative cytology report should, in general, be regarded as no report at all,⁶ particularly if there is a definite lump. In the case of a vague nodularity of the breasts, especially in young women, while a negative cytology report with few cells present might not appear as definitely benign as a negative histology report on a mass of fibrous breast tissue, one must weigh up carefully whether the surgical trauma is always justified.

With lymph nodes metastatic carcinoma is readily recognised, as is an abscess. While a malignant lymphoma may be diagnosed with confidence, particularly when it is a recurrence, it is preferable that any initial cytological diagnosis of malignant lymphoma is confirmed histologically, when classification may be more precise. A cytological report of reactive lymph nodes should be reviewed in the light of the clinical findings.

The minimal trauma caused by fine needle aspiration is one of its great advantages. Because the needle divides structures rather than cutting through them it may be used with minimal risk in the abdomen and even the chest. Biopsy at these two sites often requires a team, including radiologist and radiographer and involving expensive imaging equipment. The procedure is time consuming, sometimes taking up to an hour for one patient. Under these circumstances the technique is rather more expensive and so one may be justified in arranging a cytotechnician for the x ray department to ensure that the smears are correctly made and, even more important, that sufficient material has been aspirated. If this avoids major surgical intervention then the added trouble is justified.

The danger of false positive diagnosis has been emphasised throughout. In many ways reported fine needle aspiration cytology is similar to a frozen section report: a positive report must be backed by certainty.

Implantation of cancer cells after this technique is very rare,²⁰ and Berg and Robbins³⁹ showed identical 15 year survival rates in matched groups of fine needle and surgically biopsied patients with breast cancer. The same applies to patients with renal cancer.⁴⁰

The only contraindication to aspiration cytology diagnosis is in the diagnosis of primary malignant melanoma. It will induce inflammation which will confuse the subsequent histology, and it may facilitate deeper spread, so crucial in the assessment of prognosis.

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Requests for reprints to: Dr JV Lever, Consultant Pathologist, Royal United Hospital (North), Combe Park, Bath BA1 3NG, England.