Diagnosis of thyroid diseases – the role of the pathologist

Clinicians should work closely with cytopathologist and radiologist colleagues to achieve optimum outcomes

Pathologists are often requested to report on biopsy material obtained from patients with a solitary nodule of the thyroid, or a diffuse or multinodular goitre which may or may not be associated with a disturbance of thyroid hormone secretion.

Fine needle aspiration (FNA)

Fine needle aspiration (FNA) has become a popular technique, especially in the evaluation of solitary thyroid nodules. A solitary thyroid nodule could be a colloid cyst, a dominant hyperplastic nodule in a multinodular goitre, a follicular adenoma or carcinoma, or any other type of thyroid malignancy. FNA can be done as an out-patient procedure and is quick, inexpensive and relatively painless, with minimal risk of complications [1, 2]. Some studies have claimed a sensitivity and specificity of over 90%, so that FNA is recommended as the initial test in the evaluation of any thyroid nodule [2, 3, 4]. FNA will help to select for early surgery patients who are likely to have a thyroid neoplasm, and identify patients with a benign cytologic pattern who need follow up. Surgeons, endocrinologists and physicians, should work closely with the cytopathologist and be familiar with the reporting format and terminology used by the cytopathology laboratory. They should be aware of potential diagnostic pitfalls that may lead to false positive results, so that unnecessary total thyroidectomies and diagnostic lobectomies can be avoided. Awareness of the limitations of FNA help to minimise false negative results by repetition of the test or by resorting to histological assessment.

The cytological diagnostic categories for FNA of the thyroid include inadequate smear, benign lesion, follicular proliferation and specific diagnoses of malignancy such as papillary carcinoma, medullary carcinoma and anaplastic carcinoma.

Inadequate smears

Inadequate smears contain material that is insufficient to make a diagnosis [5]. Poor cellular yield could be due to a sampling error when the needle is not in the lesion, or faulty technique such as inadequate or excessive suction during the procedure. It also occurs in sclerotic lesions (fibrous variants of Hashimoto thyroiditis, Riedel thyroiditis and neoplasms with a fibrous stroma), lesions with thick calcified capsules, large lesions with cystic degeneration, long-standing cysts and vascular neoplasms [5]. Adequacy of the thyroid smear should preferably be judged in a clinical context, with consideration of the results of radiological investigations.

A rare group of benign follicular epithelial cells should be considered as being inadequate rather than indicative of a benign lesion. Multiple punctures of the nodule and preparation of at least 6 smears will help to minimise inadequate smears [5].

Smears with a benign diagnoses

Smears with abundant colloid, histiocytes (cyst macrophages), and a few clusters of normal-looking follicular epithelial cells indicate a benign lesion. Potential diagnostic pitfalls include presence of abundant colloid in a well-differentiated follicular carcinoma [5], and presence of large numbers of histiocytes and degenerated epithelial cells in cystic papillary carcinomas [6]. Patients with benign smears in whom clinical data suggest otherwise should have a repeat aspiration [7]. If facilities are available an ultrasound scan should be done to evaluate if a large cyst contains solid areas. Ultrasound guided aspiration of the solid area may help in the diagnosis of cystic neoplastic lesions.

Smears showing follicular proliferation

These are cellular smears with microacinar structures and scanty colloid. The follicular proliferation may be due to a hyperplastic adenomatous proliferation, follicular adenoma or carcinoma, or a Hurthle cell neoplasm. A well-differentiated follicular carcinoma can be distinguished from an adenoma only by the presence of capsular or vascular invasion. This distinction is not possible in cytologic preparations [8]. Sometimes even the distinction between a hyperplastic adenomatous nodule and a follicular adenoma can be difficult [8]. So that patients with the diagnostic category of follicular proliferation need a histological diagnosis. The diagnosis of poorly differentiated follicular carcinoma is easier because cell clusters often show irregular microacinar structures, crowding and overlapping of nuclei, coarse chromatin clumping and presence of macro- or micro-nucleoli [9].

Smears showing a specific malignant diagnosis

Papillary carcinoma is the commonest type of thyroid malignancy [10]. Cytological diagnostic features include the presence of papillary fronds, psammoma bodies, a powdery, dusty chromatin pattern and nuclear pseudo-inclusions and grooves. Thick colloid that causes a peculiar streaking and smearing effect like bubble gum [2], and the presence of eosinophilic columnar or cuboidal

cells help in the diagnosis. Most cases of false positive cytological diagnoses of the thyroid are in the category of papillary carcinoma. This is because relatively inexperienced pathologists often base the diagnosis on just one or a few of the above criteria which can occur in benign conditions also, such as Hashimoto thyroiditis [11], hyalinising trabecular adenoma [8,11] and hyperplastic goitre. The differentiation of papillary hyperplasia from papillary carcinoma in the background of Hashimoto thyroiditis can be very difficult. The fact that Hashimoto thyroiditis can be complicated by papillary carcinoma [12] adds to the confusion. Pathologists faced with this difficulty should seek a second or third opinion, or request histological assessment. In this regard it is noteworthy that the nuclear features of papillary carcinoma are sometimes seen histologically in the follicular cells of Hashimoto thyroiditis without papillary carcinoma [2]. This has led to the clinically and conceptually important claim that such areas may represent a precursor (preneoplastic) stage of papillary carcinoma [2]. The observation that close to 95% of thyroid glands with Hashimoto thyroiditis without morphologically recognisable papillary carcinoma show the RET/PTC gene rearrangement specific for papillary carcinoma tends to support this claim [13, 14].

Clinicians who are aware of the possibility of a false positive diagnosis of papillary carcinoma sometimes refer the patient to a second pathologist for a repeat FNA. This may lead to further confusion if the second pathologist does not aspirate the exact lesion. So it is better to submit the original cytology smears to a second pathologist rather than subjecting the patient to a repeat FNA. False negative diagnosis of papillary carcinoma can also occur. Smears of papillary carcinoma are known to contain monolayered tissue fragments resembling those of a follicular lesion. The monolayered fragments of papillary carcinoma often show branching, sweeping curves. Careful examination of the constituent cells will show the characteristic nuclear features [9]. A recent study has shown that individual cytologic features such as presence of bigger and more irregularly shaped nuclei, nuclear atypia, simultaneous presence of lighter staining nuclei, and apparent nucleoli are statistically related to the recurrence of papillary carcinoma [15]. Diagnosis of medullary carcinoma or anaplastic carcinoma is also possible by aspiration cytology, and the former can be confirmed by immunocytochemical studies [8].

Pathologists who are requested to perform of FNA of multinodular goitres may face the dilemma of how many areas and which nodules to sample. Ideally all palpable nodules should be sampled as any one of them could be neoplastic. An ultrasound scan will help to pick out solid lesions from colloid cysts and ultrasound guided FNA may be helpful. As mentioned previously hypercellular

aspirates from multinodular goitres may be misdiagnosed as follicular neoplasms, and hypercellular aspirates with papillaroid fragments may be misdiagnosed as papillary carcinoma. Spindle shaped stromal cells with prominent nucleoli may lead to an erroneous diagnosis of anaplastic carcinoma or medullary carcinoma [9].

Any type of thyroiditis can be mistaken for a neoplasm because of clinical and gross features such as rapid asymmetric enlargement, nodularity, firmness, and fixation to surrounding structures. FNA is useful to diagnose Hashimoto thyroiditis. Diagnostic pitfalls other than those already mentioned include presence of many Hurthle cells which may lead to a misdiagnosis of Hurthle cell neoplasm, and follicular hyperplasia in Hashimoto thyroiditis which can lead to misinterpretation as a follicular neoplasm.

Frozen section

The role of intra-operative frozen section in the diagnosis of thyroid lesions has diminished in recent years due to the use of FNA [8]. Pathologists are sometimes requested to perform frozen sections on biopsies taken from an area for extrathyroid invasion by carcinoma or metastatic lymph nodes [2]. The diagnosis is often obvious but Riedel thyroiditis, extrathyroidal growth in diffuse hyperplasia and sequestered thyroid nodules are potential diagnostic pitfalls [16].

Core needle biopsy

Core needle biopsy of the thyroid has failed to gain widespread acceptance [2]. It may be useful in the diagnosis of diffuse disease such as Hashimoto thyroiditis or diffusely infiltrating malignancies. Most pathologists are reluctant to use this technique for evaluation of solitary thyroid nodules because it is impossible to distinguish between benign and malignant follicular neoplasms using it. It also carries a small but definite risk of bleeding, nerve injury, tracheal perforation and tumour implantation [2].

Surgical biopsies (lobectomies and total thyroidectomies)

A pathologist reporting on resection specimens for malignancies is expected not only to confirm malignancy, but also to comment on prognostic factors such as presence of extrathyroid extension [17], multicentricity [2], and involvement of surgical margins. Categorisation into morphologic subtypes is important, as some morphologic subtypes of papillary carcinoma, such as the papillary microcarcinoma and the encapsulated variant, have a good prognosis [2] whereas the tall cell variant has a bad prognosis [18].

The future

Activation of the proto-oncogene RET or NTRK1 by intrachromosomal inversion or translocation is a specific change seen in papillary carcinoma [19]. Germline mutations of the RET gene are found in patients with type 2 multiple endocrine neoplasia who have medullary carcinoma, whereas 26-69% of patients with sporadic medullary carcinomas have shown somatic point mutations in the RET gene [8]. Thus molecular genetic features may play a role in the diagnosis of thyroid neoplasms in the future.

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