CASE REPORT

Worrisome histologic alterations following fine-needle aspiration of the parathyroid

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Fine-needle aspiration (FNA) is a procedure that is increasingly being performed. Artefacts occurring after FNA are reported to complicate the histological analysis of the tissue, mainly in the thyroid; WHAFFT (worrisome histologic alterations following FNA of thyroid) is well documented in the literature. The case of a male patient with hypercalcaemia who was subsequently found to have a nodule in the thyroid gland is reported here. He underwent FNA, followed by a total thyroidectomy and parathyroidectomy. The abnormality in the parathyroid gland showed worrisome histological changes that were suspicious of a malignant lesion, resembling the changes seen in the thyroid gland after FNA. Parathyroid cells were identified by a review of the previous FNA. The concept of WHAFFT, which can mimic the features of malignancy in the parathyroid gland, is therefore introduced.

Reactive changes after fine-needle aspiration (FNA) for cytology are well documented in several organs, including the thyroid,^{1–4} salivary glands^{5,6} and the breast.⁷ When these changes resemble malignancy, they have clinical implications. In the breast, such changes are recognised on a mammogram.⁷ In the thyroid gland, these changes are common and the concept of “worrisome histologic alterations following FNA of thyroid”, given the acronym WHAFFT, was proposed in 1994.¹ In contrast, FNA of the lymph nodes was shown not to influence the subsequent histopathological examination.⁸ To our knowledge, no description of the effects of FNA on the parathyroid gland exists in the literature.

We report the case of a patient with parathyroid adenoma that exhibited very worrisome features, including fibrosis, pseudoinvasive trapping and cytological atypia. The patient had an associated thyroid nodule, and a careful search through the medical history disclosed a previous thyroid FNA. A review of that aspirate identified parathyroid cells, confirming that a parathyroid lesion had been aspirated, thus explaining the unusual morphological features.

CASE REPORT

A 63-year-old man was referred to an endocrinologist for assessment of hypercalcaemia. In addition to chronic fatigue of 5 years duration, the patient had nocturia and polydypsia for around 8 months. He had no history of fractures, muscle weakness or nephrolithiasis. A review of symptoms was negative for weight loss, fever or night sweats. He had no history of calcium or vitamin D supplementation.

The patient's medical history included hypertension and gastro-oesophageal reflux, for which he was treated with perinopril and rabeprazole. He had a remote history of head and neck radiation for treatment of acne. There was no family history of hypercalcaemia or diseases suggestive of

multiple endocrine neoplasia. His mother did, however, have a history of hypothyroidism.

Physical examination was non-contributory and no neck masses were palpable. Initial blood tests yielded a mean serum calcium level of 2.86 (2.15–2.6) mmol/l with an albumin level of 43 g/l. Mean ionised calcium was 1.57 (1.15–1.35) mmol/l with a corresponding concentration of parathyroid hormone of 13.9 (1.3–5.7) pmol/l. Repeat blood tests confirmed raised calcium at 2.91 mmol/l with a 24-h urine calcium excretion of 13.16 (2.5–7.5) mmol/day. Complete blood count, electrolytes, renal function, liver enzymes and alkaline phosphatase were all within normal limits. The mean concentration of thyroid-stimulating hormone was 1.08 (0.35–5.00 MIU/l).

A sestamibi parathyroid scan showed increased uptake of a persistent nature in the middle to upper pole of the right thyroid lobe laterally, consistent with a thyroid or parathyroid nodule. Ultrasound examination of the thyroid showed the right lobe to be 6.1×2.4 cm and the left 5.6×1.5 cm. Multiple nodules were seen throughout the gland with a dominant complex cystic nodule (3×2.2×2.0 cm) in the upper pole of the right lobe. An ultrasound-guided FNA of the right thyroid nodule was carried out. The initial cytology was reported to be consistent with a colloid nodule with cystic degeneration. Four months later, the patient underwent parathyroidectomy and total thyroidectomy. The post-operative course was remarkable only for hypocalcaemia treated with oral calcium and 1,25-dihydroxy-vitamin D supplementation.

The thyroid gland showed scattered colloid nodules, one of which was partially calcified. The parathyroid gland contained a moderately circumscribed lesion that was incompletely encased by a fibrous capsule with areas of dense

Figure 1 Histological examination of the parathyroid. The enlarged parathyroid gland has central fibrosis with calcification. The residual parenchymal cells form solid nests that infiltrate the surrounding tissue.

Abbreviations: FNA, fine-needle aspiration; WHAFFT, worrisome histologic alterations following FNA of thyroid

Figure 2 Histological examination of the parathyroid. Nests of parathyroid chief cells infiltrate fibrous tissue adjacent to a dense fibrous scar with haemosiderin deposition.

Figure 3 Histological examination of the parathyroid. The fibrosis is intense and traps parathyroid cells. Haemosiderin deposition can be seen.

fibrosis showing calcification (fig 1). Multiple bands of collagen radiated from the capsule, traversing the substance of the gland and dividing it into lobules. The lobules were composed of solid nests of parathyroid chief cells (figs 2, 3). Between and around the lobules was a dense fibrotic reaction, with focal haemorrhage and haemosiderin-laden macrophages (figs 2, 3). The nuclei showed a moderate amount of pleomorphism, a coarse chromatin pattern and many cells with prominent nucleoli (fig 4). No fat was seen within or surrounding the parathyroid cells. The mitotic count was about 2 per 10 HPF. Chief cells infiltrated the surrounding fibrous tissue singularly and in small groups, simulating a malignant neoplasm (fig 3). The stellate nature of the fibrosis with reactive changes, however, raised the possibility of a prior intervention of some kind.

A review of the cytology of the previous FNA identified a population of clearly recognisable parathyroid cells (fig 5) that proved to be positive for parathyroid hormone by immunohistochemical analysis.

DISCUSSION

FNA may elicit florid reactive changes that can look ominous and sway the pathologist into entertaining a diagnosis of malignancy in the subsequent material received for histological analysis. LiVolsi was the first to describe this phenomenon in the thyroid, introducing the term WHAFFT in 1994.¹ Her findings were confirmed by subsequent authors. Pandit and Phulpagar⁴ concluded that more than 38% of thyroidectomies carried out after FNA will show features of WHAFFT, with haemorrhage and fibrosis being the most common. Worrisome changes, including nuclear atypia, vascular prominence, capsular pseudoinvasion and squamous metaplasia, can also be seen in the spectrum of WHAFFT. Ersoz *et al*² found histopathological evidence of WHAFFT in 80% of the thyroidectomies they studied after FNA. Haemorrhage was the most common feature, followed by vascular proliferation or vascular thrombus formation. Fibrosis, cystic degeneration and infarction were also seen. Some of these features vary with the time elapsed between the FNA and surgical resection. Fibrosis and pseudoinvasion are seen months to years after FNA, but it is unusual to see these changes within days or a few weeks. In contrast, acute haemorrhage is usually found shortly after FNA, and the histiocytic reaction, with accumulation of haemosiderin, persists for many weeks. Whereas the fibrosis and pseudoinvasion are the most worrisome findings, the presence of haemorrhage, haemosiderin and macrophages provides evidence of the aetiology. Fortunately, in most patients, including ours reported here, the surgical procedure is carried

Figure 4 Histological examination of the parathyroid. The cytology of the parathyroid cells is somewhat atypical with moderate nuclear pleomorphism, coarse chromatin pattern and prominent nucleoli.

Figure 5 Fine-needle aspiration of the thyroid. Nests of parathyroid chief cells are recognised by the abundant clear cytoplasm and bland nuclei.

out within several weeks to a few months after the FNA, when all of the manifestations may be found.

Similar changes after FNA have been reported in several tissues. In the salivary glands, histological changes after preoperative FNA of benign parotid salivary gland lesions include squamous metaplasia, infarction, necrosis, subepithelial stromal hyalinisation, haemorrhage, inflammatory changes with giant cells, granulation tissue, fibrosis, cholesterol cleft formation, pseudoxanthomatous reaction, pseudocapsular invasion and microcystic degeneration.⁵ In cases with exuberant squamous metaplasia, necrosis and

Take-home messages

- Reactive changes after fine-needle aspiration (FNA) for cytology are well documented in several organs, including the thyroid, salivary glands and breast.
- Clinical implications result when these changes resemble malignancy.
- Parathyroid adenomas that have undergone needle biopsy can exhibit worrisome features, including fibrosis, pseudoinvasive trapping and cytological atypia.
- The presence of these atypical features should result in recording a careful history before making the diagnosis of parathyroid carcinoma.

subepithelial stromal hyalinisation, a misdiagnosis of squamous cell carcinoma or low-grade mucoepidermoid carcinoma must be avoided. Interestingly, these features are more commonly seen in acinic cell carcinomas.⁶

The effects of FNA of the breast on subsequent mammography were studied by Horobin *et al*,⁷ who concluded that some small cancers may be obscured and other small lesions may be interpreted falsely as malignant because of the effects of FNA. As a result, the accepted practice in most medical centres has been changed, with mammography being carried out before FNA.

Some organs are not affected by FNA to the extent where a histological diagnosis can be compromised. In one study,⁸ 28 lymph nodes with reactive hyperplasia were studied for the effects of FNA before biopsy. The effects of FNA were present in 43% of lymph nodes and consisted only of needle tracts occupying 5–10% of the lymph node surface area. The authors concluded that FNA does not interfere with subsequent histological evaluation of lymphadenopathy.⁸

To our knowledge, the effects of FNA on parathyroid gland tissue have not been reported in the literature published in English. Diagnostic biopsies, however, have been recommended to confirm localisation of pathological parathyroid tissue identified at ultrasound examination or on scintigraphic localisation studies.^{9–12} Moreover, in some places, parathyroid enlargement with hyperparathyroidism has been treated with alcohol ablation.^{13–14} When this procedure fails and surgery is required, the effects of this treatment will have changed the structure of the gland.

Many features suggestive of malignancy were present in our patient—namely, dense fibrosis, pseudoinvasion of the capsule, cellular atypia, mitoses and lack of fat in the parathyroid cells. Our suspicion of a previous FNA led us to clarify the history, retrieve the previous FNA slides and review the cytology. Clusters of parathyroid cells were present. We have seen similar features in glands after alcohol ablation. The lack of relevant history in patients with a thyroidectomy can be misleading. Spontaneous infarction of parathyroid adenomas has been reported, in which the tumour showed scarring with haemorrhage and haemosiderin-laden macrophages.¹⁵ Before attributing such

changes to spontaneous outgrowth of blood supply, however, an aetiology should be sought. We therefore recommend that the presence of atypical features such as those we describe should result in a careful history of the patient being taken and that awareness of the possible cause of these changes should prevent the inappropriate diagnosis of parathyroid carcinoma.

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