Primary hyperparathyroidism with water clear cell content: the impact of histological diagnosis on clinical management and outcome

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ABSTRACT

Water clear cell hyperplasia (WCCH) and water clear cell adenomas (WCCA) of the parathyroid glands are rare causes of primary hyperparathyroidism. We report in this series one case of WCCH and two cases of WCCA representing 0.3% of patients with primary hyperparathyroidism presenting to our institution. Increased parathyroid cellular water content was responsible for relatively larger parathyroid gland sizes. However, this was not associated with higher biochemical markers or more severe clinical presentations. Histological distinction between WCCH and WCCA is difficult but important since patients with WCCH who have had a parathyroidectomy via a unilateral neck exploration may carry an increased risk of future disease recurrence.

KEYWORDS

Primary hyperparathyroidism – Water clear cells – Parathyroid hyperplasia – Parathyroid adenoma

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Parathyroid water clear cell hyperplasia (WCCH) is an extremely rare cause of primary hyperparathyroidism. It was first described in 1934 and, unlike chief cell hyperplasia, is not associated with multiple endocrine neoplasia syndromes, and it has no malignant potential.^{1,2} In order to identify the impact of this disease entity on management

and outcome, we searched our prospectively maintained database from 2000–2012 in two institutions. Histology reports of 1,017 patients with primary hyperparathyroidism were reviewed. Water clear cells (WCCs) were evident in only three cases.

Case 1

A 61-year-old woman presented with primary hyperparathyroidism. Preoperative serum calcium and parathyroid hormone (PTH) levels were 2.9mmol/l (normal: 2.1–2.6mmol/l) and 41.2pmol/l (normal: 1.6–6.9pmol/l) respectively. Sestamibi imaging suggested a large left parathyroid adenoma (Fig 1A), as did ultrasonography (Fig 1B). At operation, two large lobulated, mahogany-coloured nodules (7,000mg and 11,000mg) were removed from the left superior and inferior aspects of the adjacent thyroid gland. The right side was not explored. It was not possible to determine whether the nodules represented a single hyperplastic gland or two adjacent glands that had coalesced. Histology revealed classic features of WCCH (Fig 1C).

The patient made an uneventful recovery, and two weeks postoperatively her calcium and PTH levels were 2.2mmol/l and 4.6pmol/l respectively. The last follow-up appointment was seven months following the operation, with calcium

Figure 1 Patient 1 with water clear cell parathyroid hyperplasia: sestamibi study showing a prominent area of persistent increased activity over left thyroid gland suspicious of a parathyroid adenoma (A); ultrasonography showing a possible large left parathyroid adenoma measuring 61mm x 29mm x 25mm (B); histology showing diffuse sheets of uniform cells with eccentric small nuclei and abundant clear cytoplasm with absence of normal parathyroid tissue (C).

Figure 2 Patient 2 with a large water clear cell parathyroid adenoma: sestamibi study showing persistent increased activity over the left inferior thyroid region suggestive of a parathyroid adenoma (A); histology showing features of a parathyroid adenoma with water clear cells replacing most of the parathyroid gland except for a small compressed rim of normal parathyroid tissue (arrow) (B).

Figure 3 Patient 3 with a water clear cell parathyroid adenoma: This patient had negative sestamibi imaging. Histology showed a large nodule of water clear cells with an evident fibrous capsule separating it from adjacent normal parathyroid tissue (A). A higher magnification showed the striking distinction between normal and water clear cells on both sides of the fibrous capsule (B).

within the normal range.

Case 2

A 73-year-old man was referred from another hospital with the diagnosis of primary hyperparathyroidism. Preoperative calcium and PTH levels were 3.24mmol/l and 30.8pmol/l respectively. Both ultrasonography and sestamibi imaging were concordant in diagnosing a left inferior parathyroid adenoma.

A minimally invasive parathyroidectomy was performed and the patient was discharged on the same day. The histology report showed a 37mm x 35mm x 17mm adenoma weighing 8,000mg with predominantly WCCs compressing normal parathyroid tissue (Fig 2). The calcium level dropped to 2.4mmol/l and remained within the normal range until the last follow-up appointment nine months later.

Case 3

A 74-year-old woman was referred from another hospital with the diagnosis of primary hyperparathyroidism. The highest preoperative serum calcium and PTH levels were 2.9mmol/l and 11.8pmol/l respectively. Sestamibi imaging was negative. Ultrasonography, however, showed a 16mm x 12mm x 3mm left inferior parathyroid adenoma. Owing to lack of concordance between ultrasonography and the sestamibi study, a left open neck exploration was performed and a 900mg PTH adenoma was removed. Histology showed a water clear cell adenoma (WCCA) (Fig 3). The patient was discharged the next day and her calcium level at the 46-month follow-up appointment was 2.5mmol/l.

Discussion

Three cases of patients with hyperparathyroidism associated with evidence of WCC content on histology are presented. The incidence of WCC parathyroid disease in our series was 0.3%, which is in keeping with the declining incidence of WCCH from 13% in the 1930s to less than 1% nowadays.⁵ The incidence of WCCA, however, has always

been extremely low with only a few scattered case reports.

WCCs are not part of the composition of normal human parathyroid glands and their presence has been associated with parathyroid hyperfunction. The presence of WCCs represents transformed chief cells that have been shown to occur more frequently with advancing age.^{4,5}

Classically, WCCH starts in the superior parathyroid glands, which may reach large sizes before involvement of the inferior glands. This occurred in our first patient although it was not possible to confirm whether this was a case of a bilobular superior gland or coalescence between both superior and inferior glands. The contralateral side had not been explored as the initial diagnosis was that of an adenoma. In both our cases of WCCAs, it was the inferior gland that was involved and islands of normal parathyroid tissue were present on histological examination. Distinction between WCCH and WCCA may not always be possible owing to incomplete gland replacement by WCCs in hyperplasia or the presence of asymmetrical hyperplasia. The presence of an intervening fibrous capsule suggests an adenoma.

Contrary to previous studies showing significant clinical changes in patients with WCC disease,⁶ only one patient in our series had mild symptoms. Although all patients had elevated preoperative calcium and PTH levels, these were not proportionate to the large cell mass.⁷ This might be explained by the much lower concentration of PTH per mg of tissue in cases of WCCs when compared with chief cell adenomas/hyperplasia or even normal parathyroid cells.⁵ The correlation between gland weight and biochemistry in cases of WCCH/A is therefore not reliable. Preoperative calcium and PTH levels in this case would not be a useful guide to the tumour size. This is especially true in the presence of concomitant ipsilateral thyroid cysts, which might preclude the interpretation of the preoperative ultrasonography findings.

Follow-up showed no disease recurrence. A longer follow-up period would be indicated in the first case with WCCH since the contralateral side had not been explored. A decision to monitor the patient rather than reoperate was taken based on clinical and biochemical cure. This is in addition to the difficulty in some cases to distinguish between

asymmetrical hyperplasia and double adenomas, which might have been the case in our first patient if an adenoma had completely replaced the gland.

Conclusions

WCCH/A is a rare pathological entity with a markedly evident histological appearance. Distinction between both subtypes is sometimes difficult although clinically significant. WCCAs reach larger sizes than typical adenomas, making the operation more challenging. However, outcomes are favourable if they are completely resected. WCCH may appear similar to adenomas owing to asymmetrical enlargement of

the superior parathyroid glands leading to positive preoperative localisation and a unilateral approach. Strict follow-up is essential if bilateral neck exploration is not attempted due to the possibility of recurrence.

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