Multiglandular Parathyroid Disease in Primary Hyperparathyroidism With Inconclusive Conventional Imaging

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Summary

Inconclusive preoperative imaging is a strong predictor of multiglandular parathyroid disease (MGD) in patients with primary hyperparathyroidism (PHPT). MGD was investigated in a cohort of 17 patients with PHPT (mean age 64.9 years, total calcium 2.75 mmol/l and parathyroid hormone (PTH) 113.3 ng/l) who underwent ^{18}F-fluorocholine PET/CT (FCH) imaging before surgery. The initial MIBI SPECT scintigraphy (MIBI) and/or neck ultrasound were not conclusive or did not localize all pathological parathyroid glands, and PHPT persisted after surgery. Sporadic MGD was present in 4 of 17 patients with PHPT (24 %). In 3 of 4 patients with MGD, FCH correctly localized 6 pathological parathyroid glands and surgery was successful. Excised parathyroid glands were smaller ($p < 0.02$) and often hyperplastic in MGD than in single gland disease. In two individuals with MGD, excision of a hyperplastic parathyroid gland led to a false positive decline in intraoperative PTH and/or postoperative serum calcium. Although in one patient it was associated with partial false negativity, parathyroid imaging with FCH seemed to be superior to neck ultrasound and/or MIBI scintigraphy in MGD.

Key words

Multiglandular parathyroid disease • Primary hyperparathyroidism • ^{18}F-fluorocholine PET/CT • Persistent primary hyperparathyroidism

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Introduction

The incidence of sporadic multiglandular parathyroid disease (MGD) varies in the range of 8 to 33 % [1]. The detection rate of MGD in primary hyperparathyroidism (PHPT) is influenced by the extent of parathyroid surgery (bilateral exploration or focused parathyroidectomy), by the experience of both the operating surgeon and the pathologist, by the sensitivity of parathyroid imaging (conventional versus non-conventional methods) and also by the criteria of successful surgery [2]. Surgical cure in PHPT is defined as normocalcemia 6 months postoperatively regardless of parathyroid hormone (PTH) levels [3]. A recent article has shown that nearly one-third of patients with PHPT has persistently elevated PTH after surgery [4]. Normocalcemic PHPT is significantly associated with MGD [5,6]. Our experience showed that MGD could be one of the underlying causes of postoperative normocalcemic hyperparathyroidism.

In MGD, pathological parathyroid glands are often small and hyperplastic compared to single gland parathyroid disease (SGD) [1]. These histopathological characteristics pose a problem for imaging techniques in correct localization of all pathological parathyroid glands [7,8]. Negative preoperative imaging by MIBI scintigraphy (MIBI) and/or neck ultrasound (US) is a strong predictor of MGD in patients with PHPT [1,9].

Our aim was to analyze the presence of MGD in an extended previously evaluated cohort of 17 PHPT patients examined with ^{18}F fluorocholine PET/CT (FCH) after inconclusive first-line imaging (US and MIBI SPECT).

Methods

The clinical data of a cohort of patients with PHPT and discordant parathyroid imaging were retrospectively evaluated between 2018 and 2020. Thirteen out of 17 patients have been previously described [10], and the group was extended by four subjects to 17 in total. A patient in the previous cohort underwent a second surgery for elevated postoperative PTH, and histopathological findings from the initial surgery were reanalyzed in two other patients with persistent PHPT. Of the four new patients added to the cohort, three had SGD and one had MGD. Patient data is summarized in Table 1. Research was carried out in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study and anonymized data handling, informed consent was omitted.

Thyroid imaging by US, MIBI and/or FCH has previously been described previously [10].

Fasting blood samples were collected and total serum calcium with creatinine were measured photometrically on the Cobas 6000 analyzer (Roche Diagnostics GmbH, Basel, Switzerland) in the Department of Clinical Biochemistry of the Institute of Endocrinology. Serum intact PTH (2nd generation) concentrations were determined by the Electrochemi-luminescence Immunoassay (ECLIA), normal ranges 15-65 ng/l. Serum 25-hydroxyvitamin D (25OHD) were measured by the ECLIA to determine vitamin D status.

MGD was defined as more than one enlarged parathyroid gland excised in surgery and documented as abnormal on histopathology or excision of a single enlarged parathyroid gland, confirmed by histopathology, in a patient who remained hypercalcemic. SGD was defined as the excision of one pathological parathyroid gland with resolution of hypercalcemia [3,9].

Continuous characteristics between patients with MGD and SGD patients were compared using the Student's T-test. A p-values less than 0.05 were considered significant.

Table 1. Characteristics of patients with single and multiglandular primary hyperparathyroidism and inconclusive conventional imaging.

	Sporadic parathyroid disease		
	Single gland	**Multigland**	***p***
n	13 (76 %)	4 (24 %)	
Age (years) ± SD	64.9 ± 7.6	65.0 ± 5.0	*0.49*
Gender	12 F/ 1 M	4 F	
Total calcium (2.15–2.55 mmol/l) ± SD	2.75 ± 0.10	2.79 ± 0.13	*0.29*
PTH (15–65 ng/l) ± SD	105.3 ± 16.76	138.0 ± 39.5	*0.04*
Creatinine (45–84 umol/l) ± SD	69.31 ± 5.82	69.25 ± 13.38	*0.50*
25OH vitamine D (75–200 nmol/l) ± SD	70.8 ± 15.32	88.8 ± 14.65	*0.06*
US positive for single disease	4	1	
MIBI positive for single disease	5	3*	
*Lesion size (mm)** ± SD*	12.8 ± 4.0	8.8 ± 2.3	*0.02*
*Reoperation****	2/13 (15 %)	4/4 (100 %)	
Adenoma	12 (92 %)	4 (40 %)	
Hyperplasia	1 (8 %)	6 (60 %)	

F – Female patient. M – Male patient. PTH – Parathyroid hormone. US positive – A lesion found by the neck ultrasound. MIBI positive – An active focus found by MIBI scintigraphy. * – 2 Correct, 1 False positive. SD – standard deviation. ** – Mean of the maximal diameter. *** – Number of reoperation for persistent hyperparathyroidism. The categorical variables are expressed by the number of cases (%) and the continuous variables by the average. Comparisons between groups were made using the Student´s t-test for continuous variables.

Table 2. Preoperative and postoperative levels of total serum calcium and parathyroid hormone in 4 patients with multigland parathyroid disease.

	Preoperative		Postoperative I		Postoperative II	
	Total calcium (mmol/l)	PTH (ng/l)	Total calcium (mmol/l)	PTH (ng/l)	Total calcium (mmol/l)	PTH (ng/l)
Patient 1	2.61	123.2	2.31	100.5	2.22	56.5
Patient 2	2.79	93.7	2.75	125.1	2.29	18.3
Patient 3	2.71	118	2.71	127.3	2.36	83.5
Patient 4	3.06	217	2.87	181.1	2.73	123.8

Reference ranges total calcium 2.20–2.55 mmol/l, parathyroid hormone (PTH) 15–65 ng/l.

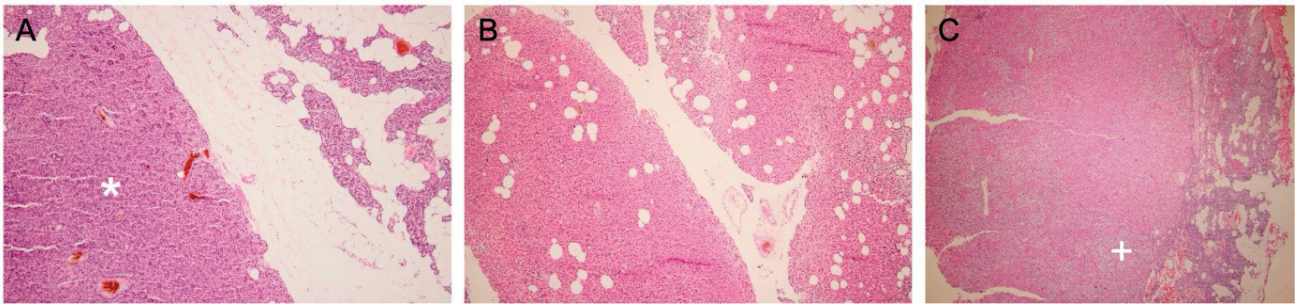

Fig. 1. Histopathological evaluation of excised parathyroid glands at the first (**A, B**) and the second surgery (**C**) in patient No. 1. (**A**) Chief cell adenoma (*) with extensive reduction of stromal adipocytes (hematoxylin eosin (HE) x 100), (**B**) Nodular hyperplasia of the oxyphilic cells (HE x 100), (**C**) Mixed cell type parathyroid adenoma containing oxyphilic and water clear cells (+) (HE x 40)

Results

In a cohort of 17 patients with PHPT (mean age 64.9 years, total calcium 2.75 mmol/l and PTH 113.3 ng/l) MGD was identified in 4 individuals (24 %) whereas 13 patients had SGD (76 %) (Table 1).

Patient No.1 has been described as No. 11 in our previous study. FCH showed, after negative MIBI and ultrasound, three active foci suggestive of enlarged upper right, lower and left upper glands. The superior parathyroid glands were found and excised in the first surgery. In the histopathological evaluation, there was one chief cell adenoma with extensive reduction of stromal adipocytes. (Fig. 1A). The second parathyroid gland was enlarged with oxyphilic cell nodular hyperplasia (Fig. 1B). Hypercalcemia normalized postoperatively but PTH remained elevated (Table 2), although vitamin D levels and renal function were normal (25OH vitamin D 81.8 nmol/l (75–200), creatinine 77 umol/l (45–84)). The right lower parathyroid gland was excised during the second surgery performed 2 years after the primary resection. In the histological investigation, a mixed cell type parathyroid adenoma was present containing almost 60 % oxyphilic cells and approximately 40 % water clear cells. (Fig. 1C). Finally, PTH normalized to 56.5 ng/l (Table 2).

In patient No. 2 MIBI scintigraphy showed an active focus corresponding to a right lower parathyroid gland with nodular thyroid disease in the right lobe. The enlarged right lower parathyroid gland (12x5x5 mm) was removed during the right thyroid lobectomy. Histopathology confirmed diffuse parathyroid gland hyperplasia, almost exclusively of the chief cells, with a reduction in interstitial adipocytes. A tiny chief cell parathyroid adenoma (0.7 mm in diameter) was found in the resected thyroid lobe. The postoperative laboratory data showed persistent PHPT (Table 2). After FCH imaging, a left upper parathyroid gland was resected and found to be an adenoma (7x5x3 mm) comprising mainly parathyroid chief cells. This patient was designated as No. 7 in our previous study and was initially believed to be a case of persistent PHPT because the MIBI imaging was false positive before the first surgery. On the other hand, the MIBI scan was partially false negative because only one enlarged parathyroid gland (right lower) was shown. Subsequent FCH imaging led to identification of

left upper parathyroid adenoma and normalization of biochemistry after the second surgery.

In patient No. 3 MIBI scintigraphy indicated a pathological left lower parathyroid gland. The neck surgeon did not find any enlarged parathyroid gland corresponding to MIBI activity and decided to explore the right parathyroid glands. Finally, an enlarged right upper parathyroid gland (10x5x3 mm) was excised and postoperative histopathology confirmed diffuse type hyperplasia, consisting predominantly of chief cells. On Day 1 after surgery, calcemia normalized but started to rise again from postoperative Day 2 and reached the preoperative level within a week after parathyroidectomy. Intraoperative PTH (ioPTH) was not available. In this case, the MIBI scintigraphy was false positive. MIBI activity corresponded to a thyroid nodule in the lower part of the left thyroid lobe. This was documented in histopathology because a total thyroidectomy was performed concurrently for nodular thyroid disease. Before the second surgery for persistent PHPT, FCH imaging showed a focus suggestive of an enlarged right lower parathyroid gland. This gland (10 mm in diameter) was removed by the second surgery (1 year after the first resection). Histopathology described diffuse chief cell hyperplasia. Postoperative hypercalcemia normalized, PTH remained mildly elevated but normalized within a year after surgery (Table 2).

In patient No. 4 ^{201}Thallium/^{99m}Tc-pertechnetate subtraction scintigraphy revealed a focus corresponding to an enlarged left lower parathyroid gland. The patient with laboratory signs of PHPT underwent surgery. An enlarged parathyroid gland (9x4x4 mm) with nodular hyperplasia was observed in histopathology. Hyperplastic nodules composed of chief and oxyphilic cells (Fig. 4A). Interestingly, ioPTH showed a significant 71 % decline in 10 minutes (Fig. 2) indicating surgical cure according to the Miami criteria [11]. However, hypercalcemia with elevated PTH persisted postoperatively (Table 2). In view of the presence of osteoporosis and nephrolithiasis, another surgical revision was recommended. Before the second surgery, FCH showed a focus suggestive of an enlarged right lower parathyroid gland (Fig. 3). The patient underwent the second surgery and an enlarged right lower parathyroid gland was removed (8x8x3 mm).

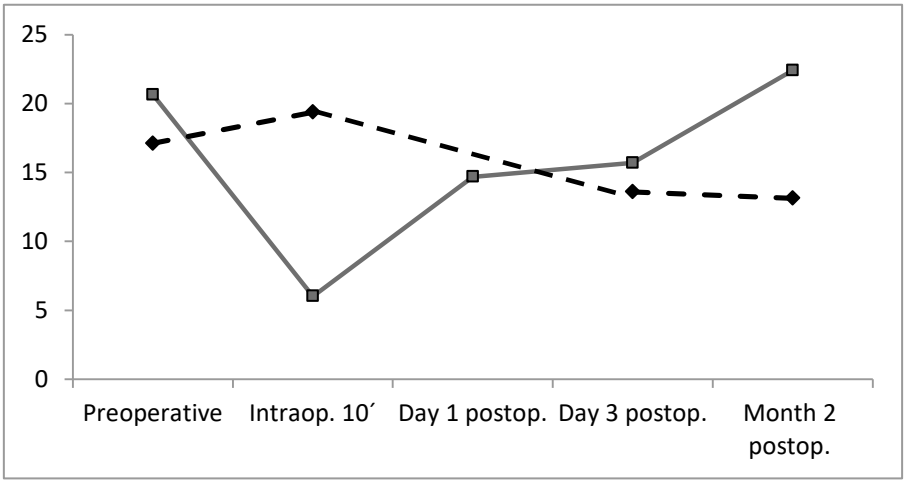

Fig. 2. Parathyroid hormone concentrations (pmol/L) in patient No. 4 after the first (solid line) and the second (dashed line) para-thyroidectomy. Postop.: post-operative, intraop. – intraoperative.

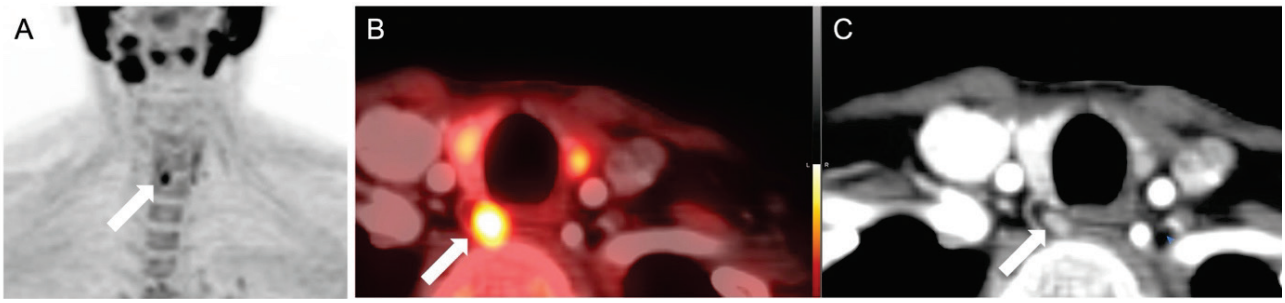

Fig. 3. ^{18}F-fluorocholine PET/CT showing focal hyperactivity dorsal to the right caudal pole of the thyroid gland (arrow), histologically confirmed as hyperplasia (patient 4, Table 2). (**A**) Maximum intensity projection. (**B**) PET/CT fusion, axial slice. (**C**) CT, axial slice.

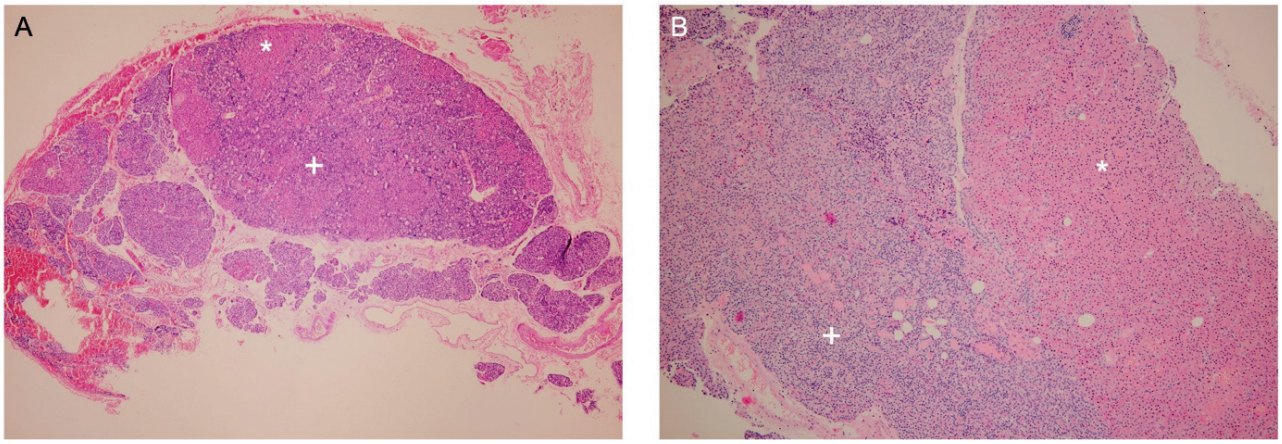

Fig. 4. Histopathology of excised parathyroid glands at the first (**A**) and second (**B**) surgery (patient No. 4). (**A**) diffuse and nodular hyperplasia of the chief (+) and oxyphilic (*) cells (HE x 40), (**B**) diffuse and nodular hyperplasia of chief (+) and oxyphilic (*) cells (HE x 100).

Excision of an enlarged pathological parathyroid gland in accordance with FCH imaging misled the surgeon to terminate the operation without waiting for the results of the ioPTH. Histopathology demonstrated a parathyroid gland with nodular hyperplasia of chief and oxyphilic cells (Fig. 4B). However, laboratory signs of primary hyperparathyroidism persisted.

Discussion

Negative preoperative imaging is a strong predictor of MGD in PHPT [1,2]. We have re-analyzed a group of patients with PHPT for the presence of MGD after collecting follow-up data and extension of the cohort with new subjects. In the current PHPT cohort with inconclusive conventional imaging and/or persistent disease, we found MGD in 24 % of our individuals.

Looking at the results of a previous analysis, FCH showed three simultaneous lesions in one patient. Two of them were excised and confirmed to be pathological parathyroid tissues. Therefore, we initially incorrectly assumed that there was only one case of MGD in our cohort. Finally, three other patients with MGD were recruited from individuals with persistent PHPT after initial surgery following MIBI imaging that was false positive or partially false negative.

In MGD the sensitivity of US and MIBI is significantly lower than in SGD [7,8]. In our cohort in four patients with MGD neck ultrasound identified only one parathyroid lesion out of 10 (lesion-based sensitivity 10 %). MIBI correctly identified two pathological foci out of 10 (lesion-based sensitivity 20 %). Frequently, MIBI parathyroid imaging was either partially false negative (showing only a single focus that gave a false impression of SGD) or false positive due to thyroid nodular disease [12]. FCH appeared to be superior to US and/or MIBI in MGD in the present study. Six pathological parathyroid lesions were correctly resected according to FCH imaging. In one patient, PHPT still persists indicating partial false negativity of FCH.

The present study has limitations. It is a retrospective study and the patient group is too small for statistical conclusions. However, patients with MGD did not differ from individuals with SGD individuals with respect to their age and/or hypercalcemia. In individuals with MGD the excised parathyroid glands were smaller in size and hyperplasia prevailed in histopathology more than in SGD in line with previous observations [1,9]. Interestingly, preoperative levels of PTH were higher in MGD than in SGD. We might speculate that higher levels of PTH levels in MGD could reflect the involvement of several parathyroid glands. Some reports, on the contrary, have documented higher serum calcium and PTH levels in SGD compared to MGD [13,14]. However, this was not confirmed by other studies [9,15]. Higher preoperative levels of PTH in our subjects with MGD did not reflect secondary hyperparathyroidism because the MGD group did not differ in serum creatinine and/or 25-hydroxyvitamin D levels from SGD patients.

Histopathological findings in our study sample documented a combination of various parathyroid lesions (simultaneous adenoma and hyperplasia) with various types of parathyroid cell types (oxyphilic and chief cells) in a single patient with MGD. This could indicate that MGD is a heterogeneous and very likely polyclonal disorder [16-18].

In patient No.1 a hypercalcemic form of PHPT changed to normocalcemic PHPT after excision of two

enlarged parathyroid glands. Biochemical values finally normalized after the third parathyroid adenoma was removed. This could show that MGD could comprise various biochemical forms of PHPT and, moreover, could be one of the underlying causes of postoperative normocalcemic hyperparathyroidism. A recent study in a tertiary hospital setting has shown that nearly a third of patients had elevated PTH levels with normocalcemia after parathyroid surgery [4]. Interestingly, individuals with elevated PTH after parathyroidectomy had a higher level of PTH at initial presentation.

An interesting question is how enlarged parathyroid glands contribute to biochemical findings in patients with sporadic MGD. In subject No. 4, removal of a pathological hyperplastic parathyroid gland led to a false positive decrease in ioPTH. Similarly, in patient No. 3 serum calcium normalized the first postoperative day but started to rise and returned to preoperative values. It is possible that a decrease in serum calcium might have stimulated another hyperplastic parathyroid gland with a lower calcium-PTH set point. This phenomenon has been described in PHPT in MEN1 syndrome as a sleeping parathyroid gland [19]. Even in hereditary PHPT, separate parathyroid tumors in an individual patient might exhibit various secretory functions although they harbor the same MEN1 gene mutation [19-21]. In sporadic MGD each enlarged parathyroid gland might have independent secretory function with different calcium-PTH set points. Therefore, in patient No. 4, ioPTH decreased by more than 50 % from baseline and met the Miami criteria for adequate gland resection [11].

All our patients with MGD have had a consultation with a clinical geneticist [22]. The analysis of a set of PTH regulating genes is currently not available. Hereditary PHPT is often multiglandular but occurs in younger age. An average age in our cohort is 64 years, more concordant with sporadic form of PHPT.

According to some authors, more stringent criteria for PTH decrease (more than 75 %) should be used in patients with recognized MGD [14]. In our patient, preoperative parathyroid scintigraphy imaging showed one hyperactive lesion in line with SGD and the surgeon did not have MGD indices of MGD and thus accepted 71 % decrease in ioPTH decrease as significant. During the second surgery, although ioPTH did not fall an enlarged hyperplastic parathyroid gland was removed. In this patient, the hyperplastic parathyroid glands from both the first and the second surgery did not differ either in size (both glands volume 0.1 ml) or histopathology. This raises the question whether all enlarged and pathological parathyroid glands are equally functional and shows that it is likely that size and histopathology of parathyroid glands might not closely correlate with their function. This could be clinically relevant because both intraoperative frozen histology and ioPTH cannot guarantee a successful operation in MGD if all parathyroid glands have not been identified [17,19]. In subject No.4, the hyperplastic parathyroid gland, excision of which did not change ioPTH, was strongly positive on FCH imaging, and fluorocholine uptake by an enlarged parathyroid gland would support functional activity [23]. On the other hand, in this patient, postoperative PTH and calcium persisted, but slightly decreased after each surgery. This would indicate that hypercalcemia and PTH levels could also correlate with parathyroid mass in MGD. Finally, the FCH imaging was associated with a partial false negativity in this individual. FCH showed only one focus corresponding to a pathological parathyroid gland, removal of which did not normalize serum calcium and PTH levels. This would suggest that there is an additional hyperfunctioning parathyroid gland left in situ and would correspond to findings of Grimaldi et al. where FCH showed sensitivity of 100 % per patient but 79 % per gland in MGD documenting partial false negativity of FCH [24]. In conclusion, sporadic MGD was present in 4 of 17 patients with PHPT who underwent FCH because conventional parathyroid imaging was inconclusive or did not locate all pathological parathyroid glands and the disorder persisted postoperatively. This is a pre-selected cohort of patients with PHPT and a complicated localization of the pathological parathyroid glands where the incidence of MGD increases. Subjects with MGD had higher levels of preoperative PTH. The parathyroid glands resected from MGD individuals were smaller and more often hyperplastic than in SGD patients. All four subjects with MGD had to undergo the second neck surgery for persistent hyperparathyroidism. Preoperative MIBI was negative or showed a single focus, leading to a false reassurance that these patients had SGD. Furthermore, in two individuals with MGD, excision of a hyperplastic parathyroid gland led to a false positive decrease in ioPTH and/or postoperative serum calcium, although PHPT persisted. Parathyroid imaging with FCH appeared to be superior to US and/or MIBI in MGD, although in one patient it was associated with partial false negativity. MGD should be suspected in PHPT with discordant conventional parathyroid imaging and/or in patients with

persistent PHPT after initial surgery. Preoperatively, besides FCH imaging, endocrinologists still lack reliable instruments to correctly differentiate SGD from MGD in patients with PHPT. Thus, in MGD, the success of parathyroidectomy still largely depends on the surgeon's experience.

Conflict of Interest

There is no conflict of interest.

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