

A Case of Reoperative Parathyroidectomy in Tandem with Coronary Artery Bypass Surgery

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ABSTRACT

Surgery remains the only curative therapy for primary hyperparathyroidism (PHPT). Successful localization of the hyperfunctioning parathyroid lesion(s) prior to surgery allows for a more focused surgical approach, especially important in reoperative patients. Surgery is recommended for most symptomatic patients and a subset of asymptomatic patients who meet specific criteria in terms of laboratory testing or who are osteoporotic. Situations may arise where hypercalcemia would pose significant morbidity in the postoperative periods of other major surgeries. Here, we report a case of tandem reoperative parathyroidectomy followed by coronary artery bypass surgery under one session of general anesthesia in a 60-year-old man with PHPT. Preoperatively, magnetic resonance imaging localized the lesion after multiple ultrasounds, technetium-99m sestamibi parathyroid scans and one bilateral internal jugular venous sampling failed to identify the hyperfunctioning lesion.

Keywords: Hyperparathyroidism, Reoperative parathyroidectomy, Parathyroid imaging, Coronary artery bypass surgery.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder with an estimated incidence of 27 to 30 per 100,000 person-years worldwide.¹ Surgery remains the only curative therapy for PHPT and is recommended for most symptomatic patients. For asymptomatic patients, current indications for surgery were developed by expert consensus at a workshop in 2002, and recently updated in 2009.^{2,3} Surgery may also be indicated in situations where hypercalcemia would pose significant morbidity in the postoperative periods of other major surgeries. Preoperative imaging studies to successfully localize the hyperfunctioning parathyroid lesion(s) have played an important role in the development of more focused surgical approaches, which are especially important in reoperative patients. Ultrasound and technetium-99m sestamibi (MIBI) parathyroid scintigraphy are the most commonly employed preoperative imaging studies and can identify the majority of lesions in PHPT. Occasionally, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography with or without CT (PET/CT) or even selective venous sampling for parathyroid hormone (PTH) are needed when both ultrasound and MIBI scan fail to identify the lesion(s). Here, we report a case of tandem reoperative parathyroidectomy followed by coronary artery bypass graft surgery (CABG) under one session of general anesthesia in a 60-year-old man with PHPT. Preoperatively, MRI localized the lesion after multiple ultrasounds, MIBI scans and one

bilateral internal jugular (IJ) venous sampling failed to identify the hyperfunctioning lesion.

CASE REPORT

A 60-year-old man was admitted for elective CABG after he sustained an event of acute coronary syndrome one month prior when cardiac catheterization revealed severe triple vessel disease. The endocrine service was consulted on the day of admission to plan for management of hypercalcemia in the perioperative period.

Review of medical records (Table 1) from the referring hospital revealed that he had longstanding (9 years duration) hypercalcemia and underwent unsuccessful bilateral cervical exploration 44 months prior to his current admission. Preoperative imaging studies completed by the time of his initial cervical exploration included three cervical ultrasounds, two MIBI scans, an MRI of the neck, and an 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging, all of which failed to localize the parathyroid lesion(s). During the prior surgery, a total of six surgical specimens were collected, but only two of them revealed parathyroid tissue on final pathological diagnosis, both of which were microscopically normal parathyroid glands. Intraoperative PTH monitoring was not utilized. After the operation, serum PTH on postoperative day 13 was still elevated at 194 ng/L (normal range: 10-65 ng/L; to convert to pg/mL, multiply by 1.0) and continued to rise to as high as 751 ng/L. His serum calcium transiently normalized

Table 1: Summary of laboratory and imaging data

	Normal range	Initial presentation 9 years prior	Period in between	Initial cervical exploration 44 months prior	Period in between	Admission for reoperative PTx Time Zero	Postoperative day 2	Current 11 months later
Laboratory Measures								
Ca (mmol/L)	2.18-2.55	2.6	2.48-3.13	2.45 ^a	2.55-4.18	2.8 ^b	1.88	2.3
Phos (mmol/L)	0.77-1.45		0.61-1.00		0.58-0.77	0.58 ^b	1.00	1.0
PTH (ng/L)	10-65		94-241	194 ^c	194-751	583.1	14.80	9
Cr (µmol/L)	44.2-97.2	88.4	70.7-106.1	Not utilized	97.2-335.9	130.8	137.90	183.9 ^e
Intraoperative PTH (ng/L)								
IJ PTH sampling (ng/L)								
L IJ: >1900 ^d								
R IJ: 1727 ^d								
Imaging								
Ultrasound			Negative x 3		Negative x 1	Negative x 1		
MIBI			Negative x 2		Negative x 1	Negative x 1		
MRI			Negative x 1		Negative x 4	A 2.3 x 3.0 cm (transverse) mass in the right tracheoesophageal groove at the cervicothoracic junction with features suggestive of cystic degeneration or necrosis, consistent with large parathyroid adenoma		
FDG-PET								
Negative x 1								

Abbreviations: Ca--calcium; Phos--phosphorus; Cr--creatinine; L--left; R--right. PTx: parathyroidectomy

Unit conversions: To convert Ca to mg/dL, multiply by 4; to convert Phos to mg/dL, multiply by 3.10; to convert PTH to pg/mL, multiply by 1.0; to convert Cr to mg/dL, multiply by 0.0113

^a postoperative day 1

^b 2 days after infusion of zoledronic acid 4 mg

^c postoperative day 13

^d 2 months prior to reoperative parathyroidectomy

^e Patient developed worsening renal function due to congestive heart failure

to 2.45 mmol/L (normal range: 2.18-2.55 mmol/L; to convert to mg/dL, multiply by 4.0) on postoperative day 1 but quickly rose to above normal and continued to rise over time to 4.18 mmol/L at its highest.

In the 3 months prior to this hospitalization, the patient was admitted twice to another hospital for acute renal failure due to hypercalcemia with a peak serum creatinine of 335.9 $\mu\text{mol/L}$ (normal range: 44.2-97.2 $\mu\text{mol/L}$; to convert to mg/dL, multiply by 0.0113) and a peak serum calcium of 4.18 mmol/L. During his second admission, ST segment depression was incidentally noted on electrocardiogram, which prompted further evaluations, including cardiac catheterization, the results of which ultimately led to the decision for CABG.

After his initial cervical exploration, one more cervical ultrasound and four more MIBI scans were performed, all of which again failed to localize the culprit lesion(s). Bilateral internal jugular (IJ) venous sampling had been done, but that too failed to lateralize the lesion (PTH was > 1900 ng/L from the left IJ and 1727 ng/L from the right IJ.)

On hospital day 2 of his current admission, MIBI scan and cervical ultrasound were repeated at the San Francisco Department of Veterans Affairs Medical Center and both failed to identify enlarged parathyroid gland(s). However, an MRI showed a 2.3 \times 3.0 cm mass in the right tracheoesophageal groove at the cervicothoracic junction with features consistent with large parathyroid adenoma (Figs 1A and B).

On hospital day 3, after careful consideration by medical and surgical teams, the decision was made to perform a combined parathyroidectomy and CABG under one session of general anesthesia. Because of preoperative localization on MRI, there was a high likelihood of successful parathyroidectomy. The cardiothoracic surgery team entered the combined procedure willing to postpone the CABG if parathyroidectomy was unsuccessful to allow further invasive parathyroid localization. The endocrine surgery team began with a focused right neck exploration. A 2 \times 4 \times 2 cm mass was identified in the right tracheoesophageal groove just inferior to the right thyroid lobe, consistent in position with the abnormal

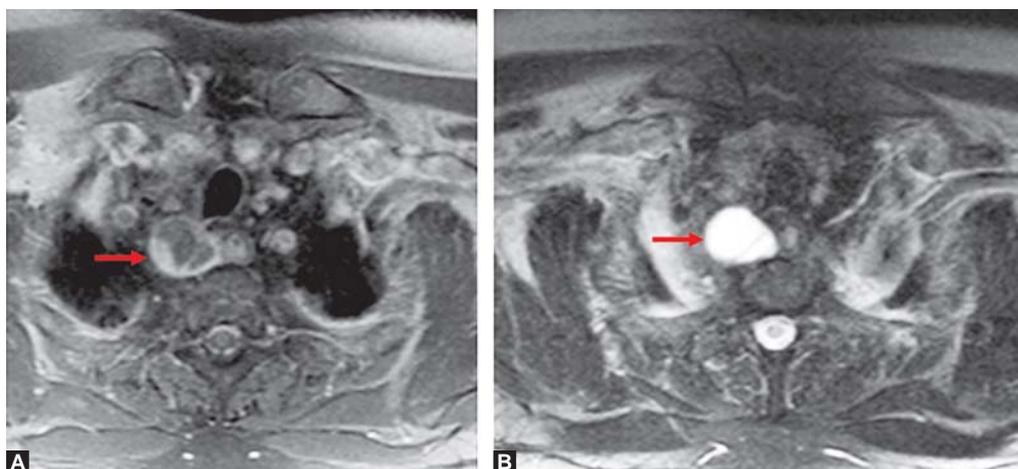
finding on the MRI. The lesion was consistent with a parathyroid adenoma, having a smooth capsule without evidence of invasion. Intraoperative baseline PTH was 1437.2 ng/L; and 10 minutes after resection of the abnormal right gland, the PTH level was 55.2 ng/L. Having removed a lesion concordant with preoperative imaging and having achieved a greater than 50% decrease in intraoperative PTH, the cardiac surgery team proceeded with an uneventful CABG. Final pathological diagnosis of the lesion was hypercellular parathyroid tissue.

Postoperatively, the patient required intravenous calcium for hypocalcemia and was discharged home on postoperative day 6 on oral calcium supplements and calcitriol. His serum PTH level was 14.8 ng/L on postoperative day 2 and 29.5 ng/L on postoperative day 20. At the time of this writing, 14 months after his operation, the patient is doing well on calcium supplements with no recurrence of hypercalcemia.

DISCUSSION

Preoperative Imaging Studies

While the biochemical evidence for persistent PHPT is indisputable in this case, multiple imaging studies at the first institution failed to localize the abnormal parathyroid gland(s). This is consistent with published data on the sensitivities of various imaging modalities in preoperative evaluation of PHPT. Sensitivities of ultrasound have been reported to range from 42 to 92%.^{3,4} Sensitivities of MIBI scan have been reported to range between 40 and 90%, and that of CT or MRI were similarly between 46 and 87%.^{3,4} PET with or without CT scan (PET/CT) can occasionally identify parathyroid adenomas in patients with persistent or recurrent PHPT when other localization studies are negative or equivocal. However, the technique is limited because (F-18) fluorodeoxyglucose is most enhanced in fast growing tumors and also concentrates in the thyroid.⁴ The wide range of sensitivities probably reflects the spectrum of skill and expertise among individual operators and/or institutions in different reported series. On the other hand, these data also suggest that a subset of cases can fail to localize



Figs 1A and B: A 2.3 \times 3.0 cm mass in the right tracheoesophageal groove at the cervicothoracic junction (arrowhead) on MRI. (A) T1-weighted postcontrast image showing a well-circumscribed heterogeneously enhancing mass with internal septation. (B) T2-weighted image showing homogeneous cystic mass with internal septation

with these imaging studies, even in institutions with a large volume of endocrine surgery. The sensitivities of different imaging modalities to localize hyperfunctioning parathyroid lesions are even lower in the subset of reoperative surgical patients.⁵

Many studies have reported that MIBI scans have higher accuracy for localization of adenomas when compared with anatomic imaging techniques.⁶ Technetium-99m sestamibi, the tracer used in MIBI scans, is a lipophilic cation which diffuses passively across the cell membrane and then gets sequestered in mitochondria by a large negative transmembrane potential. It accumulates more in adenomas than in normal parathyroid tissue due to increased vascularity and a higher number of mitochondria-rich oxyphil cells in tumor tissue. A positive correlation between sestamibi uptake and oxyphil cell content has been reported,⁷ while others have suggested that gland size and volume are also positive factors contributing to sensitivities of MIBI scans.⁸ However, false-negative results have been reported with large adenomas while some very small adenomas have been detected.⁹ The expression of P-glycoprotein (P-gp) or multidrug resistance-associated protein 1 (MRP1) by parathyroid cells have been reported to contribute to false-negative results of MIBI scans.^{9,10} Both P-gp and MRP1 are transmembrane lipoproteins that enhance the efflux of sestamibi out of parathyroid cells. However, subsequent research has been inconclusive with some showing a strong correlation between P-gp and/or MRP1 expression and false-negative results of MIBI scans¹⁰⁻¹² while others negating such correlation.¹³ Still others have reported decreased sensitivity of MIBI scans with the use of calcium channel blockers.¹⁴ Our patient was given one dose of amlodipine on the morning of his MIBI scan during his admission for parathyroidectomy and CABG. Additionally, in the prior two years, he had filled a 90-day prescription of amlodipine twice. It is possible that amlodipine could have been one of the contributing factors for his persistently negative MIBI scans.

Selective Venous Sampling in Reoperative Parathyroid Surgeries

In the minority of patients where preoperative imaging studies fail to identify the hyperfunctioning parathyroid lesion(s), experts^{5,15} have recommended selective venous sampling (SVS) for PTH as the next step in localization studies, especially in persistent and/or recurrent PHPT when the surgeon needs to operate in a scarred reoperative field.

The methodology for SVS was initially reported by Bilezikian et al in 1973.¹⁶ In their initial series, the femoral vein was cannulated and catheter was advanced distally into the thyroid vein plexus. Under imaging guidance, samples were taken from the thyroid (including superior, inferior and medial thyroid veins bilaterally) and large cervical veins, hepatic, renal and iliac veins. A ratio of concentration of PTH in a neck vessel to that in the peripheral circulation of at least 2:1 was considered a positive test. The series showed that large vein sampling was

much less helpful in localizing disease (sensitivity of 24%) compared to thyroid vein sampling (sensitivity of 80%). Using similar methodology, several more recently published series of reoperative cases showed superior sensitivity of SVS to non-invasive imaging modalities ranging from 75 to 93%.¹⁷⁻¹⁹

While SVS may prove helpful in a subset of reoperative patients, it is invasive and available only at institutions with expertise in interventional radiology. Direct bilateral internal jugular venous sampling (BIJVS) through percutaneous cannulation, on the other hand, is a much less invasive procedure that can be performed in the surgeon's office and may, therefore, provide a reasonable alternative. BIJVS was initially employed intraoperatively (after induction of general anesthesia but before surgical incision) by Ito et al to assess its utility in localization.²⁰ Using a difference of > 5% in PTH between right and left internal jugular vein samples, they showed that BIJVS had a sensitivity of 80% in localizing hyperfunctioning parathyroid lesion(s); however, BIJVS successfully localized the lesion in only 57% of the patients with negative MIBI scans. Since then, several other groups have evaluated the diagnostic accuracy of BIJVS with conflicting results.^{21,22} In our patient, BIJVS failed to localize the lesion. However, BIJVS is still a relatively new approach to preoperative localization. As experience with BIJVS advances, it will become clear whether the performance of BIJVS will improve and when it may be most appropriate to employ BIJVS.

Combined Parathyroidectomy and CABG

It is not uncommon to discover hypercalcemia due to PHPT in patients who have coronary artery disease and are under consideration for CABG. In fact, there is considerable debate regarding the association between PHPT and cardiovascular morbidity and mortality with conflicting data from epidemiological studies of patients with various degrees of disease severity.^{23,24} In the Norwegian Tromso Study involving a population of 27,159 subjects,²⁵ serum PTH was found to be an independent predictor of coronary artery disease. However, randomized controlled trial data are lacking to demonstrate causality and improved cardiovascular morbidity and mortality in the long run after correction of PHPT.

Before answers to these questions are available, clinicians are often faced with the decision of whether or not to surgically correct PHPT prior to CABG in the acute setting. While mild hypercalcemia may be managed medically with saline hydration and loop diuretics, moderate to severe hypercalcemia in post-CABG patients would be riskier to manage due to the need for aggressive saline hydration and the administration of potentially nephrotoxic drugs (i.e. intravenous bisphosphonates). The degree of hypercalcemia in our patient does portend significant postoperative morbidity, including renal failure and cardiac arrhythmias in the face of major fluid shifts post-CABG. In addition, this patient had already required two admissions for medical management of symptomatic hypercalcemia. Our approach of tandem parathyroidectomy followed by CABG is

safe and has the key advantages of a single general anesthetic with invasive cardiac monitoring, timely correction of hypercalcemia, and minimal delay in revascularization of diseased coronary arteries.

Historical Perspective

PHPT was first diagnosed in the United States in 1926, by Eugene F DuBois. The patient was Captain Charles Martell, a mariner who had become disabled by demineralization of the skeleton over many years. Finally, a parathyroid adenoma was removed at the seventh operation in 1932.^{26,27} His case, like ours, demonstrates the difficulty, even in experienced hands, of locating a parathyroid tumor.

CONCLUSION

To our knowledge, this is only the second reported case of combined parathyroidectomy and CABG in the literature.²⁸ It illustrates the difficulty in localizing the parathyroid lesion(s) in PHPT. However, with persistent efforts at localization, parathyroid surgery can be performed safely even as a reoperative case in combination with CABG, and thus significantly reduce post-CABG morbidity and provide added benefits to the patient.

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