

Miami Criterion for Recurrent Men-1 Related Hyperparathyroidism in the Forearm

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Case Report

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Abstract

Background

Total parathyroidectomy with autotransplantation of parathyroid tissue to the forearm is one of the treatment modalities for primary hyperparathyroidism (PHPT) in multiple endocrine neoplasia type 1 (MEN 1). Recurrence rate with this approach has been documented in up to 35% of patients. The amount of tissue to be preserved during autograft debulking has not been well established.

Methods

Preoperative assessment begins with biochemical confirmation of recurrent PHPT. Anatomic and functional imaging must be obtained. Intraoperative PTH monitoring is used to evaluate adequate amount of parathyroid tissue to be debulk pursuing more than 50% of PTH drop.

Results

One patient with recurrent MEN1 related PHPT successfully underwent autograft debulking using the Miami criterion to assess adequate resection. The postoperative course was uneventful and on follow up the patient did not develop hypoparathyroidism.

Conclusion

The use of Miami criterion during autograft debulking reoperations in the setting of MEN-1 is a feasible tool to achieve remission of primary hyperparathyroidism.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome characterized by a mutation in the *MEN1* gene located at chromosome 11q13. This syndrome has an autosomal dominant pattern of inheritance. The *MEN1* gene encodes a 610 amino acid protein, *menin*, which is deeply involved in transcriptional regulation.¹ The clinical characteristics of MEN1 include the development of multiple tumors in different endocrine glands: parathyroid asymmetric hyperplasia, entero-pancreatic endocrine tumors and pituitary tumors.²

Primary hyperparathyroidism (PHPT) will be present in > 95% of patients with MEN1 diagnosis, and it is the initial manifestation in 60–90% of patients.³ The classic clinic manifestations of PHPT include fatigue, constipation bone pain, depression, nephrolithiasis among others. It is well known that in recent years PHPT presents as an asymptomatic entity in the majority of cases, this is because it is detected on routine laboratory work as isolated hypercalcemia.⁴

Parathyroidectomy is the treatment of choice for MEN1 associated PHPT.⁵ As mentioned before, multiple gland involvement is the responsible for this condition in MEN1 patients, contributing to high risk of

persistent or recurrent PHPT. The surgical treatment for MEN1 associated PHPT recommended is open bilateral neck exploration. There are different strategies to achieve optimal results: less than subtotal parathyroidectomy, subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. The main goals when treating this group of patients are to obtain normocalcemia, decrease the incidence of permanent hypoparathyroidism and decrease the number of operations that the patient will need. In order to achieve optimal results it is critical to choose the best surgical strategy.⁶

When the results among different surgical strategies are compared, subtotal and total parathyroidectomy with autotransplantation result in durable control of MEN1 associated PHPT and have longer recurrence free periods in comparison with more conservative resections. On the other hand, total parathyroidectomy with autotransplantation has a higher incidence of severe hypoparathyroidism compared with subtotal parathyroidectomy.⁷ For this reason and according to the most recent Clinical Practice Guidelines for MEN1 subtotal parathyroidectomy is suggested as the initial management of PHPT in MEN1, but total parathyroidectomy with autotransplantation may also be considered in some cases, like patients with extensive disease either at first or at repeat surgery.³

Recurrent MEN1 associated PHPT is diagnosed in 33 to 35% after initial operation, with higher recurrence rate in less than subtotal parathyroidectomy (46 to 50%) and lower recurrence rate in total parathyroidectomy and autotransplantation (6 to 35%). Reoperation of recurrent MEN1 associated PHPT is recommended when associated symptoms or complications are present.⁸⁻¹¹

In the reoperation scenario the goals are the same as those established for the index operation, specifically obtain normocalcemia and decrease the incidence of permanent hypoparathyroidism. Autograft debulking in patients with recurrent MEN1 associated PHPT who were initially treated by total parathyroidectomy and autotransplantation is not a frequently practiced procedure. The balance between autograft debulking extension and permanent hypoparathyroidism should be pursued and the implementation of a well-established technique could be helpful. For this reason, we started using the Miami criteria to intraoperative assessment of adequate tissue debulking. These criteria were described to predict operative success during minimally invasive parathyroidectomy.

Technique

Preoperative biochemical work-up should be performed similar for any form of recurrent PHPT. This algorithm includes the determination of serum or ionized calcium, PTH levels, vitamin D, and 24 hours urine calcium excretion. Once biochemical diagnosis is confirmed, anatomic and functional imaging is performed to localize recurrent neck hyperfunctioning or ectopic parathyroid tissue. If no ectopic or recurrent hyperfunctioning parathyroid tissue is localized in the neck, surgical treatment will be directed to the autograft area in the forearm.

During surgery, quick intraoperative PTH measurement protocol requires two intravenous lines, one on each arm and proximal to the autograft area. The procedure is practiced under local anesthesia and

sedation. Pre anesthesia PTH levels are obtained from both arms. An incision is made in the site of the previous autotransplantation surgery and dissection through the skin and subcutaneous tissue is made until reaching the *brachio radialis* muscular fascia. The fascia is incised, and gentle dissection is made to localize parathyroid tissue, usually marked by non-absorbable sutures or surgical clips. It is suggested to start debulking parathyroid tissue progressively and evaluate intraoperative PTH levels to avoid leaving insufficient parathyroid tissue. To avoid hypoparathyroidism, a 3–5 mm diameter remanent parathyroid tissue should be left in-situ.

Outcomes

A 22-year-old-woman previously diagnosed with multiple endocrine neoplasia type 1 (MEN-1) presented to the endocrine surgery clinic for evaluation of recurrent hypercalcemia. She had history of pancreatic insulinoma treated with laparoscopic distal pancreatectomy in December 2015.

During follow up, biochemical diagnosis of primary hyperparathyroidism (PHPT) with initial serum calcium of 14.7 mg/dL and parathyroid hormone (PTH) of 524 pg/mL was established. ^{99m}Tc SPECT/CT, showed no ectopic parathyroid tissue in the neck or mediastinum. In January 2016, neck exploration was indicated. During surgical exploration, five parathyroid glands were identified, two in normal position in the left side and three in the right side (two in normal position and a supernumerary right inferior gland). Four parathyroid glands were resected leaving one complete macroscopically normal gland (PIV) *in situ*. Serum calcium levels remained above normal and persistent hyperparathyroidism was diagnosed with PTH 454 pg/mL and serum calcium of 11.9 mg/dL. ^{99m}Tc SPECT/CT showed hypermetabolic tissue in right superior lobe. In March 2016 a neck exploration was performed. During this surgery, it was not possible to identify the right PIV gland, thus, an *en bloc* resection of the right thyroid lobe was performed. The specimen was inspected in the operating room and the PIV gland was identified firmly adhered and to the right thyroid lobe. Frozen section biopsy confirmed parathyroid tissue. The rest of parathyroid tissue was transplanted to the left forearm implanting four pieces of 1 mm each in the brachioradialis muscle.

Normal calcium and PTH levels were reported immediately and in the following months after the operation (calcium 8.8 mg/dL, PTH 6.2 pg/mL). Thirty-six months after forearm auto transplantation, serum calcium and PTH levels progressively rose (11.9 mg/dL vs. 196 pg/mL in the right arm). Functional studies demonstrated no hypermetabolic tissue in the neck, and magnetic resonance imaging confirmed active parathyroid tissue in the left brachioradialis muscle (Fig. 1A).

Left brachioradialis muscle exploration was indicated and performed in November 2019 under local anesthesia, with debulking of three pieces of parathyroid tissue that were marked in the previous operation with non-absorbable suture and metallic clips. A < 5 mm parathyroid tissue remnant was left in the brachioradialis muscle (Fig. 1B). Simultaneous serial samples were taken from the transplanted and non-transplanted arm for quick Intraoperative PTH essay measurements (Access Intact PTH immunoassay system®) during resection. Exploration and resection were guided by the behavior of

intraoperative PTH levels. Intervention was deemed complete when > 50% decrease in PTH levels at 15 minutes after partial tissue resection in the left arm was reported (Fig. 2).

At postoperative-day 1, patient presented without clinical signs of hypocalcemia and was discharged home. On follow up at 4 months, the patient was clinically stable with mild residual hyperparathyroidism, calcium 10.4 mg/dL, PTH 64.8 pg/mL, phosphorus 3.5 mg/dL and albumin 3.54 g/dL. Histological examination of the resected specimens confirmed three implants, all compatible with hyperplastic tissue. The patient decided not to go to the subsequent follow-ups.

Discussion

Primary hyperparathyroidism is a common clinical manifestation of MEN-1 patients. Standard surgical treatment consists of subtotal parathyroidectomy or total parathyroidectomy with forearm auto transplantation. Recurrence rates for this latter technique has been reported from 6 to 35%. Once recurrence is documented and cervical or other ectopic locations of parathyroid tissue are ruled out, surgical treatment should be directed to the autograft site. The AMOUNT of parathyroid tissue to be preserved in order to achieve eucalcemia and avoid hypoparathyroidism is not clearly defined.

There are some reports of radio guided surgery for forearm reinterventions in patients with recurrent disease associated with secondary hyperparathyroidism.¹²⁻¹⁴ Two of them describe the use of both radioguided parathyroidectomy with intra operative gamma probe and intraoperative PTH monitoring. In one case the patient was found to be hypercalcemic 2 weeks after the intervention¹² with the second remaining normocalcemic with PTH levels within normal parathyroid function one year after debulking surgery.¹³

The Miami criterion was first described to predict postoperative eucalcemia in patients with sporadic PHPT. This criterion predicts operative success of 98% aiming for a > 50% PTH drop from highest pre-precision or pre-excision hormone level in a peripheral blood sample obtained 10 minutes after complete resection of all hyperfunctioning tissue.¹⁵

Since the pathophysiology responsible for parathyroid hyperfunctioning is different between sporadic PHPT, secondary hyperparathyroidism and MEN1 related PHPT; the use of the Miami criterion has not been validated comparing this patient populations. A retrospective cohort study by Lambert et al. including 37 patients with MEN1 related PHPT described two cases of recurrent PHPT requiring autograft debulking. This group uses intraoperative USG imaging to locate the autograft and intraoperative PTH assay, not specifying the criterion used to predict success.¹¹

It is expected that our patient will develop recurrent hyperparathyroidism, and this event will not be surprising. It has been demonstrated that parathyroid hyperplasia in MEN1 patients could be driven by the bFGF, which is a potent endothelial cell mitogen found in a variety of normal and tumor tissues.^{16,17} This is a humoral growth factor that may promote hyperplasia of the parathyroid tissue autograft.

Nevertheless, the main goals in this scenario are to have a considerable time lapse between normocalcemia and recurrence without hypoparathyroidism in the interim. This technique proposes a novel application of the Miami criterion in the reoperative setting of MEN1 related PHPT, to avoid iatrogenic hypoparathyroidism in this setting. Further use and validation of quick ioPTH protocols in large MEN1 cohorts is pending.

Declarations

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- iii. Ethics approval: A written consent was obtained from the patient.
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Figures

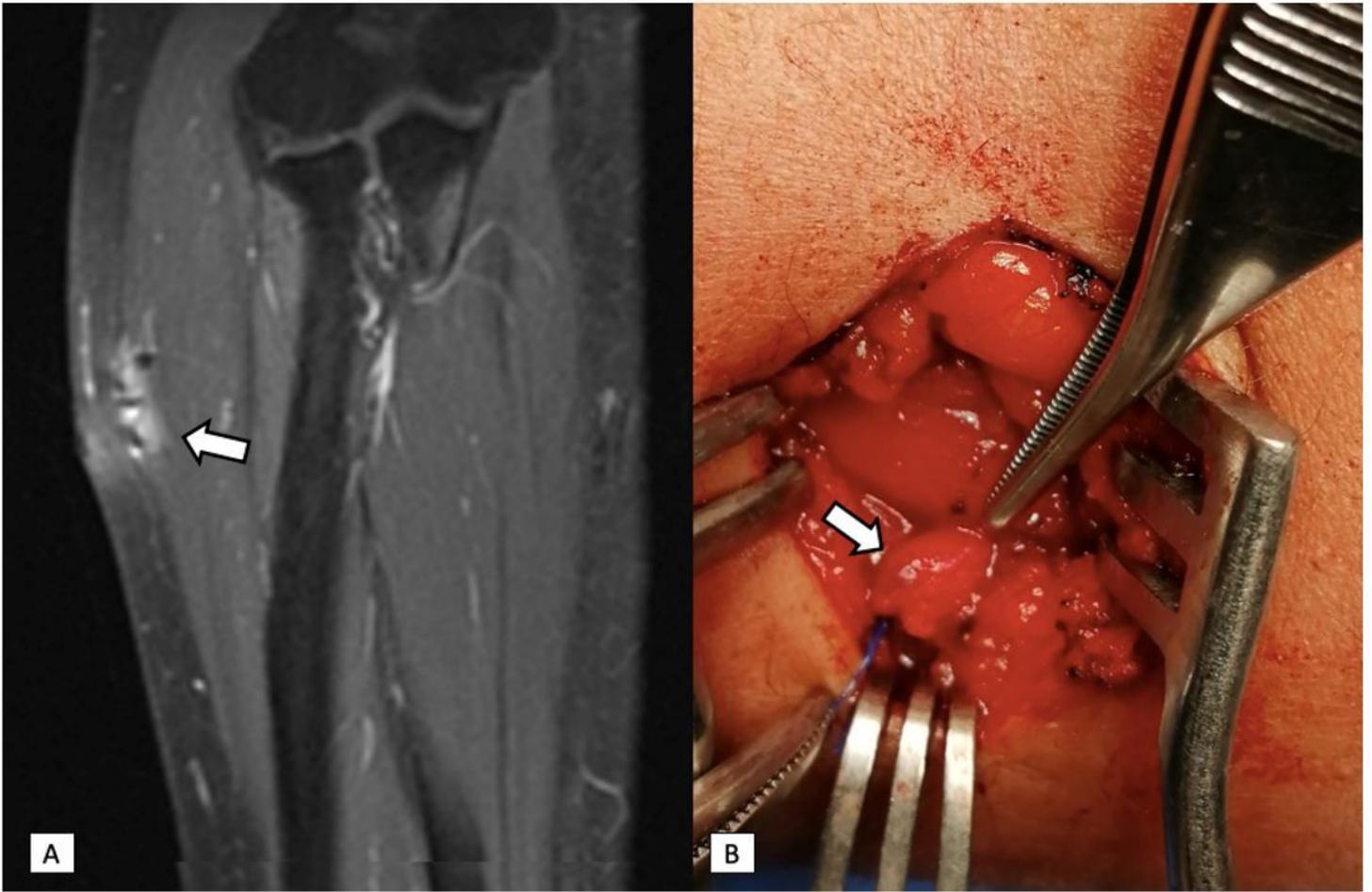


Figure 1

A) Magnetic resonance showing parathyroid tissue in the left brachioradialis muscle. B) Intraoperative imaging of parathyroid tissue in the brachioradialis muscle

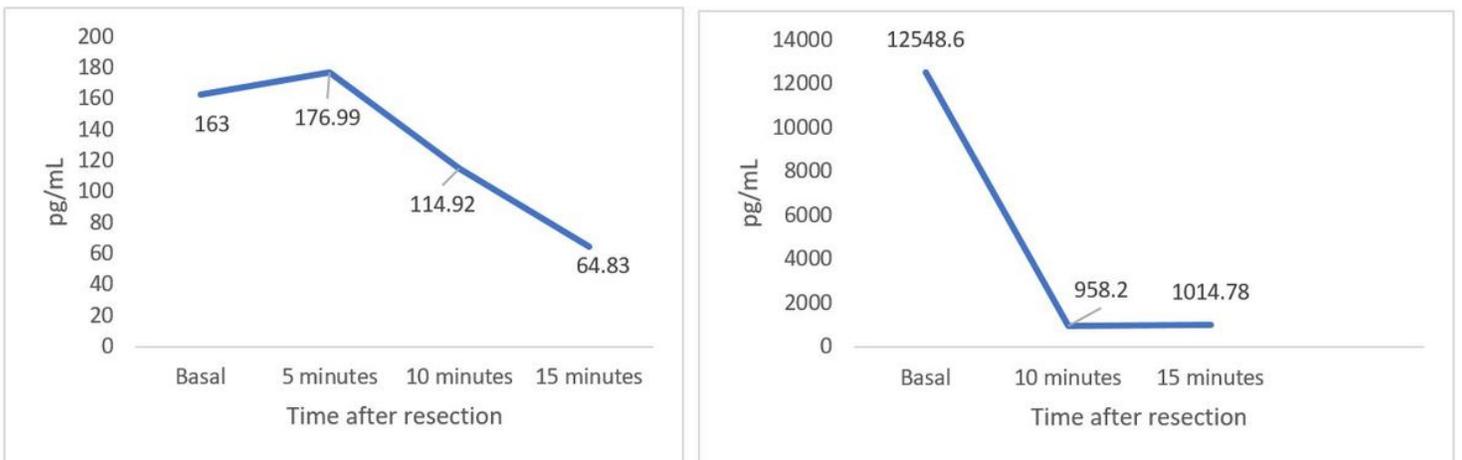


Figure 2

Intraoperative parathyroid hormone monitoring, A) right arm, B) left arm (autograft)

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