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Secondary Hyperparathyroidism: Diagnosis of Site of Recurrence

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Persistent or recurrent hyperparathyroidism after total parathyroidectomy with forearm implant may be caused by hyperplastic grafted tissue, residual parathyroid tissue left in the neck or the presence of a supernumerary gland not found during surgery. A correct assessment of graft function is needed to localize the source of hormone excess and to avoid an unnecessary neck reoperation in cases of graft dependent hyperparathyroidism. In 12 patients with relapsing hyperparathyroidism after total parathyroidectomy with forearm implant, total ischemic blockade of the arm bearing the parathyroid graft produced a "transitory implantectomy" with a significant reduction of serum levels of intact PTH in those with graft hyperfunction. In 6 patients with proved supernumerary glands, total ischemia of the graft was not followed by significant changes in intact PTH. Hyperparathyroidism was reversed after surgical resection of the parathyroid implants in the 6 patients with positive responses to the ischemic maneuver. A repeat neck reoperation removing cervical or mediastinal supernumerary glands was followed by control of recurrent hyperparathyroidism in the 6 patients with a negative response to the ischemic blockade. Total ischemic blockade of the arm bearing the parathyroid graft is a valuable new method for a correct assessment of graft function after total parathyroidectomy with forearm autotransplantation.

Secondary hyperparathyroidism is a frequent complication of chronic renal failure. Pruritus, muscular pain, osteitis fibrosa and fractures frequently present in patients with severe secondary hyperparathyroidism. Resistance to vitamin D treatment, in the absence of aluminum excess, is an indication for parathyroidectomy to control the disease [1–4].

The aim of surgery is to reduce the parathyroid mass in an attempt to obtain normal mineral metabolism. The amount of residual parathyroid tissue left in place is difficult to determine. Since the persistence of chronic renal failure enhances recurrence in some patients, subtotal parathyroidectomy (PTX) sometimes requires a neck reoperation, with the subsequent high surgical morbidity [5–7].

Total PTX with autotransplantation of parathyroid tissue is a well accepted treatment in the control of vitamin D resistant secondary hyperparathyroidism [8–11]. Hypoparathyroidism and recurrence are complications associated with this surgical procedure. Postoperative hypoparathyroidism can be prevented by transplantation of a portion of cryopreserved glands [12] and recurrent hyperparathyroidism can be controlled by resection of a part of the hyperfunctioning graft under local anesthesia [13].

Persistent or recurrent hyperparathyroidism after total PTX with forearm implant can present a difficult diagnostic problem. The source of excess PTH could be from either hyperplastic grafted tissue, residual parathyroid tissue left in the neck, or a supernumerary gland not found during surgery [13, 14–16].

Several diagnostic procedures have been employed to localize the source of PTH excess after failed surgery. Isotopic studies with thallium technetium subtraction scanning, computed tomography, magnetic resonance imaging and high resolution ultrasonography have a low sensitivity [17]. Studies on the parathyroid hormone gradient in the blood draining the graft bearing arm versus the contralateral arm have also failed, independently of the assays used to recognize the PTH molecule [12].

Control of recurrent or persistent hyperparathyroidism after total PTX with forearm implant needs a correct assessment of graft function in order to avoid either unnecessary resection of grafted parathyroid tissue or an unnecessary neck exploration.

The half life of intact parathyroid hormone has been found to be less than five minutes [18]. Complete ischemic blockade of the arm bearing the graft could reflect in a few minutes acute PTH changes in cases of graft dependent hyperparathyroidism.

We present in this report a series of patients with recurrent hyperparathyroidism in which the blockade of parathyroid graft function allowed the correct diagnosis of the site of hyperfunctioning parathyroid tissue to be made.

Patients and Methods

Twelve patients under dialysis treatment who had undergone a total parathyroidectomy with forearm autotransplantation in two different hospitals (Paris and Santander) presented with evidence of hyperparathyroidism 0.5 to 10 years after surgery. Surgical technique had been performed in the standard manner. Neck exploration demonstrated the presence of 4 parathyroid glands which were removed in each patient. The thymus was removed, too. Between 12 and 15 pieces of 1 mm size and a total weight of 150–200 mg were prepared from one gland. The parathyroid tissue was autotransplanted in the muscle of the

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Table 1. Clinical and biochemical data of patients.

Patient	Age	Sex	Time after PTX (yrs)	Total calcium (mg%)	iPTH	Normal value
1	61	M	4	10.3	22	<10 pmol/l
2	55	M	3	10.5	26	<10 pmol/l
3	40	M	3	9.9	33	<10 pmol/l
4	33	M	2	10.0	42	<10 pmol/l
5	68	F	10	8.6	700	<60 pg/l
6	54	F	9	11.2	925	<60 pg/ml
7	44	F	6	11.5	68	<10 pmol/l
8	56	F	0.5	11.4	21	<10 pmol/l
9	55	M	9	8.2	640	<60 pg/ml
10	36	F	7	8.4	1.390	<60 pg/ml
11	69	M	9	8.2	845	<60 pg/ml
12	47	F	6	8.6	950	<60 pg/ml

PTX = parathyroidectomy; iPTH = intact parathyroid hormone.

arm contralateral to the arteriovenous fistula. Each pocket containing 3–4 pieces of parathyroid tissue was identified with a stitch of prolene for subsequent identification.

All of the patients had higher than normal PTH levels (2–20 times the normal level). Patients 7 and 8 had persistent hypercalcemia, and the remaining patients had either bone pain and/or radiological or histological evidence of bone resorption (Table 1). In order to determine the source of PTH secretion, the patients were submitted to an ischemic blockade study.

Ischemic Blockade

Patients gave informed consent for the test. The arm bearing the parathyroid graft was submitted to total ischemia under intravenous regional analgesia [19]. This anesthetic technique is routinely used for surgery of the hand. Patients were monitored for arterial blood pressure and continuous EKG tracing. An arm vein was cannulated with a thin catheter. Two pneumatic orthopedic tourniquets 7 cm–wide were applied around the proximal end of the limb and connected to an inflation pump (BIOMET 855/AMK2). Exsanguination of the limb was achieved by means of an Esmarch bandage. The proximal tourniquet was inflated up to 100 mm Hg over the basal systolic blood pressure. Lack of radial pulse was assessed. Lidocaine 0.5% at a dose of 3 mg/kg was slowly injected. If the patient complained of tourniquet–induced pain, then the distal tourniquet was inflated and the proximal deflated. Ischemia of the arm was maintained for 30 minutes. Duplicate blood samples for intact PTH were obtained from the contralateral arm before and during the ischemic period (10, 20 and 30 min) and 10 min after ischemia.

PTH Assays

Intact parathyroid hormone was assayed in 6 patients (Santander, Spain) using N-tact PTH RIA kit (INCSTAR Corporation, Stillwater, Minnesota, U.S.A.) with an upper limit in normal subjects of 10 pmol/l. Intra–assay coefficient of variation was 8%. In 6 patients (Paris, France) intact PTH hormone was assayed using the N-tact PTH IRMA (INCSTAR Corporation, Stillwater, Minnesota, U.S.A.) with a normal range up to 60 pg/ml. Intra–assay coefficient of variation was 4%. Correlation coefficient between the two intact PTH assays was r:0.97.

Results

All patients included in the study showed high serum levels of intact PTH after total parathyroidectomy with autotransplantation. Changes in PTH levels after arm ischemia are shown in Table 2. In 6 cases (patients 1 to 6) intact PTH levels in the non–grafted arm had a significant decrease (more than 46%) during the graft bearing arm ischemia. When blood flow was restored intact PTH levels increased up to basal values. Total surgical excision of macroscopic parathyroid hyperplasic graft tissue was followed by the immediate correction of hyperparathyroidism.

In the remaining 6 cases (patients 7 to 12) there were slight changes in intact PTH levels after ischemia of the graft bearing arm (a decrease lower than 20% of the basal values). They were submitted to surgical neck re–exploration. Supernumerary missed cervical (4 cases) and mediastinal (2 cases) glands were found at surgery. Hyperparathyroidism was reversed after reoperation in 5 cases. In case number 10, in spite of the persistence of PTH levels over the normal range, there was a more than 80% reduction of PTH levels after surgery, with disappearance of bone pain.

No clinical complications were recorded either during the arm ischemia or during follow-up (6 to 24 months).

Discussion

Autotransplantation of parathyroid tissue after total parathyroidectomy is an accepted technique to maintain adequate secretion of parathyroid hormone [8], but this procedure can be followed by either hypoparathyroidism (non–functioning graft) or recurrent hyperparathyroidism.

Recurrent hyperparathyroidism due to graft hyperplasia can be controlled by graft excision, a simple procedure of minimal risk. However, the existence of recurrent hyperparathyroidism may be due to residual areas of parathyroid tissue left in the neck or to the presence of a supernumerary gland not found at surgery. Consequently, a correct reoperation requires precise localization of the source of hormone excess. Isotopic and PTH gradient studies are not always conclusive, and graft excision is not always followed by a reduction in PTH levels.

In the present study, 6 of 12 patients with hyperparathyroidism after total PTX with autotransplantation showed a 46% to 87% reduction in PTH levels after 10 to 20 minutes of arm ischemia. Two to 6 weeks after total graft excision, PTH levels were within the normal range in 5 patients, and slightly elevated in 1 patient. In all of them, persistence of some PTH secretion was evident in spite of a "total" PTX and "total" macroscopic graft excision. Residual areas of parathyroid cells in the neck or in the arm could explain such a secretion. On the other hand, in the remaining 6 patients who proved to have a supernumerary gland, ischemic blockade produced only a maximal decrease of 20% of basal PTH values. This decrease could be due to the blockade of some PTH graft dependent secretion. Persistence of graft hyperfunction could coexist with a residual cervical gland, as in case 10, with probable graft related hyperparathy-

Table 2. Changes in PTH levels after arm ischemia.

Patient	Pre	Ischemia 10 min.	Ischemia 20 min.	Ischemia 30 min.	Post 10 min.	PTH maximal reduction[a]	Diagnosis	PTH 2–6 weeks after reoperation
1[b]	22	15	12	14	20	46%	GH	6
2[b]	26	10	8	9	31	70%	GH	5
3[b]	33	13	12	13	32	64%	GH	13
4[b]	42	15	12	17	36	72%	GH	6
5[c]	700	180	160	140	820	80%	GH	20
6[c]	925	130	125	135	975	87%	GH	undetectable
7[b]	68	64	54	63	65	20%	5th C	9
8[b]	21	19	19	21	22	10%	5th M	10
9[c]	640	530	525	690	675	18%	5th C	undetectable
10[c]	1390	1150	1175	1225	1330	18%	5th C	120
11[c]	845	705	720	705	510	17%	5th C	undetectable
12[c]	900	885	910	870	890	3%	5th M	undetectable

GH = graft hyperplasia found at reoperation; 5thC = cervical 5th gland found at reoperation; 5thM = mediastinal 5th gland.
[a]Lowest PTH value obtained during the ischemia expressed as percentage of basal value.
[b]PTH expressed in pmol/l, normal value <10 pmol/l.
[c]PTH expressed in pg/ml, normal value <60 pg/ml.

roidism after the 5th cervical gland removal. Follow-up studies are needed to confirm these preliminary results.

To the best of our knowledge the method here proposed has not been described previously. It is very simple and non-invasive. It will improve the follow-up of patients submitted to total parathyroidectomy with forearm implant, and of those with recurrent or persistent hyperparathyroidism in particular. Though we induced ischemia for 30 minutes without problems, we think that 10–15 minutes ischemia is adequate for the correct assessment of the test.

Résumé

La persistance ou la récidive de l'hyperparathyroïdie après la parathyroïdectomie totale avec réimplantation de tissu parathyroïde dans l'avant-bras peut être due soit à l'hyperplasie du tissu transplanté, soit au tissu parathyroïde cervical oublié ou méconnu, soit à la présence d'une glande surnuméraire. Pour éviter une réexploration du cou inutile, nous préconisons de faire un bilan de la fonction du greffon avec localisation de la source exacte de l'excès de production hormonale. Chez 12 patients ayant une hyperparathyroïdie récidivante après parathyroïdectomie totale avec réimplantation parathyroïde dans l'avant-bras, le test de l'ischémie provoquée de l'avant-bras par garrot déclenchait une réduction transitoire mais importante du taux de parathormone (PTH) intacte dans le sérum chez les patients avec greffon hyperplasique. Le taux de PTH n'a pas varié chez 6 patients qui avaient une hyperparathyroïdie en rapport avec une glande parathyroïde surnuméraire prouvée. Chez 6 autres patients, l'ablation du greffon a normalisé les taux de PTH. Une nouvelle exploration cervicale ou médiastinale supérieure pour enlever les glandes surnuméraires a réussi à normaliser les taux de PTH lorsque l'ischémie provoquée de l'avant-bras était nēgative. L'ischémie provoquée du bras porteur du greffon est une manoeuvre nouvelle utile pour évaluer la fonction du greffon après auto-transplantation dans l'avant-bras.

Resumen

El hiperparatiroidismo persistente o recurrente después de paratiroidectomía total con implantación en el antebrazo puede ser causado por hiperplasia del tejido trasplantado, por tejido paratiroideo residual en el cuello o por la presencia de una glándula supernumeraria no identificada en el curso de la operación. Es necesario determinar la función del trasplante a fin de ubicar la fuente de la producción excesiva de hormona y evitar reoperaciones innecesarias en el cuello en casos de hiperparatiroidismo dependiente del trasplante. En doce pacientes con hiperparatiroidismo recurrente después de paratiroidectomía total con implante en el antebrazo, el bloqueo isquémico total del brazo que contiene el trasplante produjo una "implantectomía transitoria" con reducción importante del nivel sérico de HPT intacta en los paciente con hiperfunción del trasplante. En seis pacientes con glándulas supernumerarias demostradas, la isquemia total del trasplante no resultó en cambios significativos del nivel de HPT intacta. Se logró la reversión del hiperparatiroidismo después de la implantectomía quirúrgica en los seis pacientes que presentaron respuesta positiva a la maniobra isquémica. Una nueva reoperación cervical para resecar glándulas supernumerarias cervicales o mediastinales resultó en el control de hiperparatiroidismo en los restantes seis pacientes con respuesta negativa al bloqueo isquémico. El bloqueo isquémico total del brazo que contiene el trasplante paratiroideo es un valioso y novel método para la correcta valoración de la función del trasplante después de paratiroidectomía total con autotrasplante en el antebrazo.

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Invited Commentary

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Total parathyroidectomy and autotransplantation has become the procedure of choice in the treatment of renal hyperparathyroidism. Numerous retrospective studies and 1 recent prospective randomized trial have shown the advantages of this procedure compared to subtotal parathyroidectomy [1]. Failure of the parathyroid autograft and recurrence caused by either residual tissue in the neck or hyperplastic tissue at the graft site can occur, but are both rather rare [2]. One of the problems in the management of patients with recurrent disease is localization of the hyperfunctioning tissue to be able to plan surgery. This surgery is easy to perform when the source of hormone excess is the autografted tissue but it means major surgery if there is recurrence caused by parathyroid tissue left behind in the neck. For localization of parathyroid glands in the neck, ultrasound, thallium-technetium scan, CT scan, and MRI, have been used with their known limited value in reoperative cases. To detect hyperplastic tissue in the forearm, one can be successful by just palpating the area of the autograft or using near range ultrasound, thallium scan or measurement of PTH levels in the antecubital vein proximally to the graft compared to those in the contralateral side. The indication for these localization procedures and for reoperation in these patients are the same as for recurrent primary hyperparathyroidism, i.e., either significant hypercalcemia or recurrence or persistance of severe symptoms and signs of the disease, like bone pain, soft tissue calcification or high levels of alkaline phosphatase.

The authors of this article added to the known localization procedures a new and intriguing technique which could be a very intelligent solution to the problem just outlined. The method of excluding the graft bearing forearm temporarily from the circulation under local anesthesia can be considered safe since it has been used by hand surgeons for a long time. According to the authors, it was able to reliably discriminate between excess parathyroid hormone being secreted in the neck versus graft borne hypersecretion.

In a clinical setting, in addition to hormone levels and their changes one would like to know more about simple tests performed in the same patients. In how many who had a graft dependent recurrence was the hyperplastic tissue in the forearm palpable? In how many was the graft demonstrable by near range ultrasound or thallium scan? In our own experience in 8 of 9 patients with graft dependent recurrence, 1 or more hyperplastic tissue particles were palpable and could be visualized by ultrasound. In 4 patients, a thallium scan of the graft bearing arm displayed the tissue [3]. A correlation of the new method described with at least palpation (probably the gold standard) would have been of major interest.

It would also be important to know more about results to be able to compare these the results of other studies. When the authors describe that the excision on the graft side "was followed by immediate correction of hyperparathyroidism", they most likely mean decrease of PTH. One would at least like to know about the pathology report on the specimen excised. Did it say that hyperplastic tissue had been removed? Has there been a decrease of serum calcium levels in the patients who were hypercalcemic and did symptoms improve? There were actually only 2 patients in 12 who were found to be hypercalcemic before reoperation. Ten had been operated on for other reasons. Our approach to the indication for reoperation is rather restrictive. We would recommend reoperation, especially in the