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Modified percutaneous ethanol injection of parathyroid adenoma in primary hyperparathyroidism

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Summary

Surgery is the treatment of choice for symptomatic primary hyperparathyroidism; unlikely few patients do not meet established surgical criteria or have comorbid conditions that prohibit surgery.
In these subjects, medical therapy alone offers little hope for a sustained long normocalcemic period. However percutaneous ethanol injection (PEI) may represent an alternative therapeutic procedure. It is currently in use for the treatment of secondary or tertiary hyperparathyroidism, however, few studies or case reports suggest it for the treatment of primary hyperparathyroidism. Moreover, little information is available about the long-term follow-up, where incomplete necrosis or the spreading of ethanol in the surrounding tissues is often reported. We believe that many of the side effects could be correlated to procedure itself. Taking these experiences into account, we have reasoned that in order to limit these side effects, we had to modify the standard PEI procedure.
We reported this preliminary experience describing our modified PEI procedure.

Introduction

Surgery is the treatment of choice for symptomatic primary hyperparathyroidism[1] except in rare cases where the surgical approach is not suitable because of technical difficulties and/or exceedingly high anaesthesia risk.[2,3] However, in these latter patients, medical therapy alone offers little hope for a sustained control of hypercalcemia.[4] Percutaneous treatment of a parathyroid adenoma by absolute ethanol injection (PEI) may represent an alternative therapeutic approach.[5] This procedure was first described by Solbiati and Colleagues in 1985[6] and has been mainly used in the treatment of secondary or tertiary hyperparathyroidism.[7–15] A small number of studies suggest that PEI may also be used for the treatment of selected cases of primary hyperparathyroidism,[3,16–23] although incomplete inactivation of the excessive parathormone (PTH) incretion or spreading of ethanol in the surrounding tissues has been reported;[24] moreover, little information is available concerning the long-term results of the procedure. We present here the results of our experience by using a modified PEI procedure in the treatment of primary hyperparathyroidism, including a follow-up up to 4 years.

Patients

First patient

A 68-year-old female was seen in our department in March 2004 for hypercalcemia. Her past medical history consisted of four episodes of neck surgery treatments: the first was at the age of 14 years for a brachial cyst; the second was thirty years

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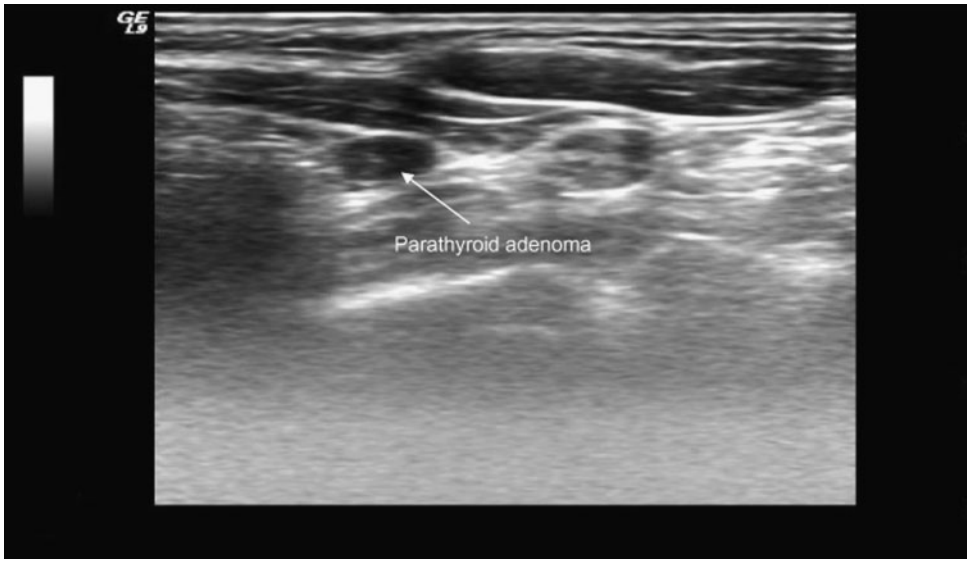

Figure 1. Ultrasound investigation: hypoechoic tissue suggestive of parathyroid adenoma.

later when she was submitted to a hemithyroidectomy, followed by radical surgery for a follicular thyroid carcinoma; then five years ago, at the age of 63 years, the patient underwent surgical exploration of the neck for hyperparathyroidism, but no pathological parathyroid tissue was found; at that time, a dual energy X-ray absorptiometry (DEXA) of the spine and hip showed a significant osteoporosis (*T*-score of −3.4). On admission, the patient appeared to be suffering from osteoarthritis. Laboratory investigation showed high levels of alkaline phosphatase (242 mU/ml, normal range 30–85), serum calcium (11.7 mg/dl; normal range 8.5–9.5) and PTH (201 pg/ml, normal range 12–72). Neck ultrasound investigation (Figure 1) showed an area of hypoechoic tissue (volume of 11.6 ml), suggestive of a parathyroid adenoma, while DEXA (spine-hip) showed persistent signs of osteoporosis (*T*-score of −3.58). Our surgeons, in consideration of the repeated surgery to the neck, considered the patient at high risk for recurrent laryngeal nerve injury and overall surgery failure; consequently, she refused further surgical treatment. We informed the patient about the possibility of using PEI for the treatment of the parathyroid adenoma and she agreed, with a written consent.

Second patient

In July 2006, a 47-year-old female was admitted to our department with hypercalcemia and pulmonary embolism. She had been previously evaluated at the Radiation Oncology unit, where she received radiotherapy treatment following the resection of a glioblastoma. Laboratory investigation showed high levels of alkaline phosphatase (357 mU/ml), serum calcium (12.6 mg/dl) and PTH (401 pg/ml). An ultrasound examination showed the presence of hypoechoic tissue in the left neck compartment, suggestive of a parathyroid adenoma (volume of 14.8 ml). Immunochemical PTH assay performed on a parathyroid fine-needle aspiration biopsy confirmed the diagnosis of primary hyperparathyroidism (PTH = 93.000 pg/ml). Taking into account the underlying clinical condition, we suggested that the patient should be submitted to PEI, and she agreed by signing written consent.

Methods

Ultrasound investigation was performed using an ultrasonographic scanner (LOGIC 9, General Electric, Milwaukee, WI, USA) equipped with a 10–14 MHz linear transducer for morphological study. The volume of the parathyroid was calculated with the standard formula for ellipsoid volumes. The PEI was performed with the patients in the supine position. No topical anesthetics or sedatives were used. The injection was made free hand, while an experienced ultrasonographer guided the procedure. We devised a modified two-step procedure. The first step was intended to create a solid fibrosis, visible at ultrasound as hyperechoic tissue, around the capsule of the adenoma by using low ethanol doses; to this purpose, after skin sterilization, a 25-gauge stylet needle was introduced into the parathyroid adenoma and guided by real-time ultrasound to the edge of the lesion; then, 0.5 ml of sterile 95% ethanol was introduced under the capsule of the adenoma while monitoring the

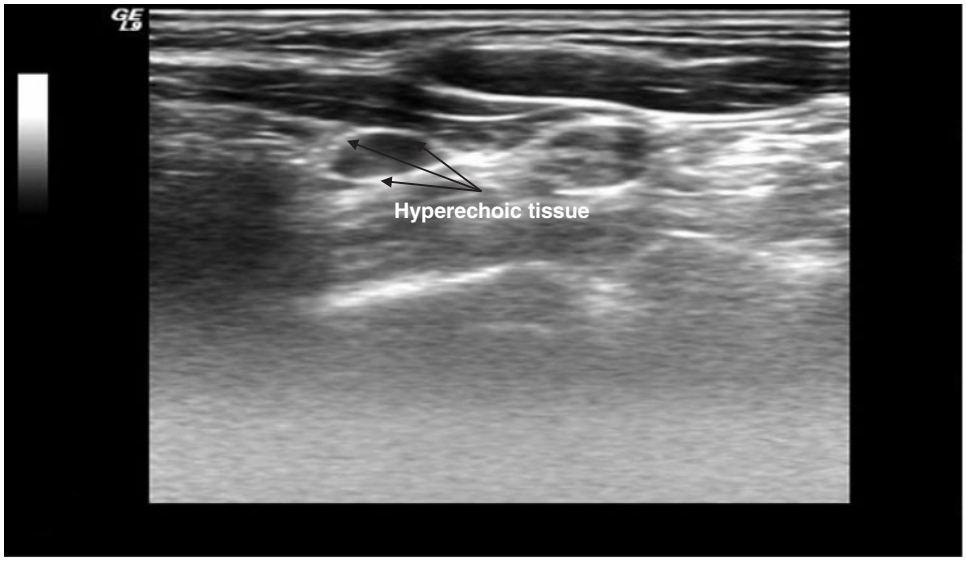

Figure 2. Ultrasound features after the first 'step': hyperechoic image all around the parathyroid adenoma.

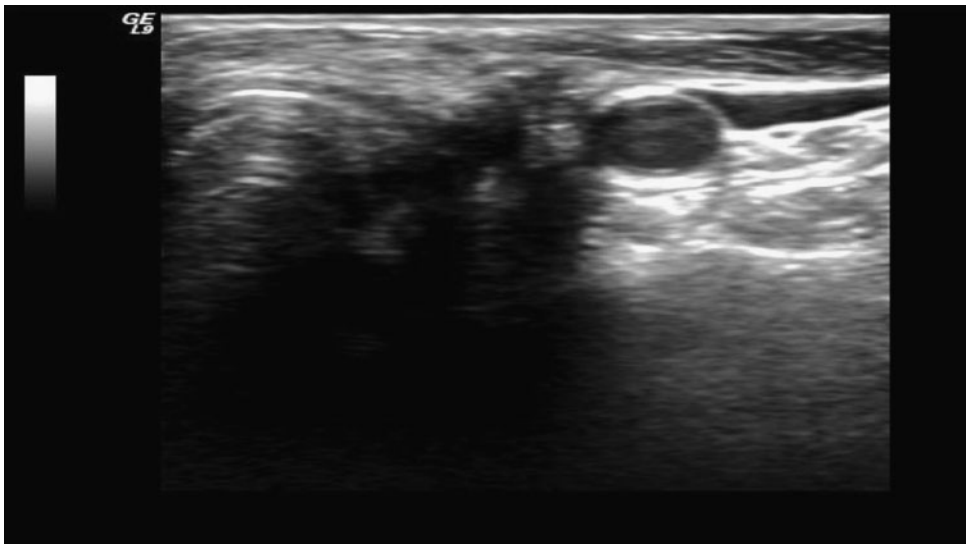

Figure 3. Ultrasound after 20 months of follow-up.

diffusion of ethanol by ultrasound. After the needle was withdrawn, each patient was observed for 10 min. This procedure was first performed in the posterior section of the adenoma and then repeated several times (5–7) around the whole perimeter of the lesion, at ten days intervals. The second step was intended to introduce ethanol (80–85% of the volume of the lesion) at the centre of the lesion, in order to destroy the adenoma with a reduced risk of alcohol spreading in the surrounding tissues.

Results

In order to obtain a visible hyperechoic 'wall' surrounding the adenoma, which would be compatible with fibrosis (Figure 2), it was necessary to repeat the first procedural step five times, at 10 days intervals. Two weeks after completing the preliminary step, we injected ethanol (80–85% of the calculated nodule volume) at the centre of the adenoma. The first patient did not complain of any pain or discomfort. One month thereafter, a calcium replacement therapy was necessary for the treatment of hungry bone syndrome. Neck ultrasound performed after 36 months of follow-up did not show any residual of the adenoma (Figure 3). Table 1 summarizes the laboratory findings before each injection and during the follow-up. The patient is currently (46 months after PEI) asymptomatic for osteoarthritis and DEXA investigation of

Table 1 Laboratory findings before each injection and during follow-up (case 1)

	I Step					II Step	Follow-up	
	1°	2°	3°	4°	5°		1st month	45th month
Serum calcium (mg/dl)	10.4	9.9	10.3	10.1	10.4	10.3	8.0	8.9
Ionized calcium (mg/dl)	6.2	5.9	6.1	6.1	6.3	6.2	1.0	4.7
Intact PTH (pg/ml)	186	145	157	163	177	162	35	49

Table 2 Laboratory findings before each injection and during follow-up (case 2)

	I Step							II Step	Follow-up
	1°		3°	4°	5°	6°	7°		(17th month)
Serum calcium (mg/dl)	12.6	10.3	12.2	12.2	11.7	12.0	12.1	11.6	8.4
Ionized calcium (mg/dl)	7.2	6.2	7.0	7.0	6.9	7.0	6.9	6.0	4.5
Intact PTH (pg/ml)	401	162	393	363	405	374	359	362	42

spine and hip shows a significant improvement in *T*-score (−1.9).

The same procedure was performed in the second patient; in this case, seven alcohol injections were necessary at the preliminary treatment step in order to obtain a satisfying peripheral fibrosis of the adenoma. Table 2 summarizes laboratory findings before each injection and during the follow-up. The patient deceased of relapsing glioblastoma 22 months after PEI; the last available measurement of calcemia, 1 month before dying, was 8.4 mg/dl.

Discussion

Primary hyperparathyroidism caused by a single benign parathyroid adenoma is the most common cause of chronic hypercalcemia[3,25,26] and parathyroidectomy represents the current treatment of choice.[3,25–28] In the few patients not suitable for surgery, medical therapy alone offers little hope for long-term normocalcemia,[3,25–30] and thus far no drug has been approved by the Food and Drug Administration for the treatment of primary hyperparathyroidism.[3] Therefore, in selected cases, PEI could represent an alternative therapeutic procedure. Indeed, PEI was introduced for the management of parathyroid hyperplasia in the early 1980s,[6] and many reports from that era describe its use in secondary or tertiary hyperparathyroidism.[7,9,11,13,15,31] Recently, the Japanese Society for Parathyroid Intervention has published PEI guidelines in chronic dialysis patients.[1] On the other hand, the role of percutaneous alcohol ablation in the treatment of primary parathyroid adenomas is not well established.[3,16,17,19] Incomplete necrosis of the adenomatous lesion has been reported[24] and little information is available about the long-term results of this procedure; in addition, spreading of ethanol to the surrounding tissues leading to the development of extraglandular fibrosis that may interfere with subsequent surgery has also been described.[5,17] Harman *et al.*[19] reported that patients treated by PEI for primary hyperparathyroidism and followed over a 16-month period, redeveloped hypercalcemia in 67% of cases and/or had recurrent laryngeal nerve injury in 5.5%. More recently, Karstrup *et al.*[23] showed similar results.

Indeed, after reviewing data from the literature, it appears that side effects are most likely related to the amount of alcohol injected: in most cases a single shot procedure with a large volume of ethanol was performed.[5,6,16,17] Taking these experiences into account, we reasoned that in order to limit these side effects, we had to modify the standard PEI procedure. We aimed firstly to create a fibrotic wall around the adenoma in order to avoid ethanol spreading at a subsequent administration of a large dose of ethanol; at the same time, the development of perilesional fibrosis could possibly contribute to reduce the vascularisation of the adenoma. As reported here, repeated injections of small doses of ethanol all around the adenoma were able to induce an evident perilesional demarcation (Figure 2) without modifying the PTH and calcium serum levels of patients (Tables 1 and 2). The number of micro-injections necessary to obtain the

desired effect may vary in relation to the size of the adenoma: five injections were sufficient in the first patient presenting a lesion volume of ~12 ml, whereas seven injections were performed in the second case, carrying an adenoma of about 15 ml. Nevertheless, it is important to emphasize that the patients did not complain of any pain or discomfort. We have also shown that the injection of a high ethanol volume at the subsequent step is well tolerated and safe, a finding that is at some variance with the experience reported by Karstrup *et al.*[17] Finally, the validity of the modified PEI procedure has been well documented by the persistent normalization of PTH and calcium serum levels through the longest follow-up period described thus far and confirmed by the result of DEXA in the first patient, showing a significant reduction of the *T*-score over the time.

In conclusion we believe that our modified PEI technique may be considered a suitable alternative for the treatment of primary parathyroid adenoma in selected patients, when the surgical approach is not feasible or refused. Further investigation on a larger series of patients is warranted to better assess the overall efficacy and safety of the proposed procedure.

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