ULTRASOUND-GUIDED PERCUTANEOUS ETHANOL INJECTION THERAPY IN A 92 YEAR-OLD PATIENT WITH PARATHYROID ADENOMA AND WITH A HISTORY OF TOTAL THYROIDECTOMY FOR PAPILLARY THYROID CARCINOMA

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Abstract

Percutaneous Ethanol Injection Therapy (PEIT) of parathyroid adenoma under ultrasound guidance is individually used as an alternative procedure in management of primary hyperparathyroidism in polymorbid elderly patients with increased surgical risk. The treatment is also suitable for patients who already underwent surgery of the thyroid gland, and any other surgery is associated with a higher risk of postsurgical complications.

We present a case of a 92-year-old male patient, who underwent thyroidectomy for papillary thyroid carcinoma three years ago. Part of the regular annual follow-up visits was also ultrasonography, which showed a solitary parathyroid adenoma at the site of the removed thyroid gland. Given the underlying condition, polymorbidity and age of the patient, the PEIT method was successfully used in the therapy. The coincidence of adenoma and papillary thyroid carcinoma is also interesting.

Key words: parathyroid adenoma, Percutaneous Ethanol Injection Therapy, papillary thyroid carcinoma.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the third most common endocrine disease and the frequency of its detection gradually increases. According to data from 2009, worldwide prevalence ranges from 0.1 to 0.7% (1). Asymptomatic cases of PHPT prevail at present, which is defined by moderately elevated serum calcium levels (s-Ca), often borderline or slightly elevated levels of serum parathyroid hormone (s-PTH) and lack of clinical manifestations. In the United States and many other developed countries, for the last 30 years, asymptomatic form represents up to three-fourth of all diagnosed PHPT cases, ratio men to women 3:1, with a maximum incidence at the age of 50-60 years (2). In the Czech Republic there is one case per 1,000

hospitalized patients, with the highest frequency among women in the age group of 40-60 years (3).

Most cases (80%) of PHPT are caused by a solitary parathyroid adenoma (PAd), 2-4% by multiple parathyroid adenomas, 15% by hyperplasia of all the four parathyroid glands and in about 0.5% of cases by parathyroid carcinoma (2).

The primary therapeutic procedure includes surgical intervention - parathyroidectomy. But since the late 1980s, sclerotherapy of PAd with 96% ethanol - Percutaneous Ethanol Injection Therapy (PEIT) is used in some cases, in specialized centers as an alternative non-surgical method. 96% ethanol causes thrombotic occlusion of blood vessels in the adenoma and subsequent necrosis and fibrosis of the tissue (4). The PEIT method under ultrasound (US) guidance was used for the first time in 1985 by Italian authors Solbiati *et al.* in the treatment of PAd in a patient with secondary hyperparathyroidism (5). In German literature the first documented case report dates back to 1987; it was an 81 year-old woman who underwent repeated US-guided PEIT applied to a PAd size 25×13×11 mm. In the first unilocular deposition of ethanol into the adenoma was with no effect on the levels of s-Ca and s-PTH, and later multilocular injection into the PAd proved successful effect and normalization of laboratory findings (6). In the United States, the first case report was reported in 1988 when a successful US-guided PEIT was performed at the Mayo Clinic (7). In both cases the method was offered as an alternative to surgery in high risk patients with PHPT.

We present a case report of a successful US-guided PEIT procedure in a 92 year-old male patient with a solitary PAd. According to literature, it has been the oldest patient case published so far. Also coincidence with papillary thyroid carcinoma (PTC) is also interesting. The PAd was identified during the

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regular annual US follow-up of the patient 3 years after total thyroidectomy for PTC.

CASE REPORT

A 92 year-old patient had been long treated for coronary heart disease with paroxysmal atrial fibrillation, hypertension, underwent cholecystectomy 10 years ago. Three years ago the patient underwent total thyroidectomy (TTE) for locally invasive PTC (pT1, Nx, Mx; size 17x12x15 mm; Fig. 1) in multinodular goiter. Surgical treatment was followed by radioiodine therapy with a dose of 3.94 GBq of ^{131}I and regular follow-up at the clinic of nuclear medicine in the University Hospital.

In the third year after TTE during the regular

Figure 1. Papillary carcinoma with multiple foci of invasion into the desmoplastic stroma (arrows). Figure courtesy of Tomas Tichy, MD, PhD.

annual US follow-up with a high-resolution linear array transducer 10MHz (Philips iU22) a small solid lesion with homogeneously hypoechoic structure was found in the bed after the left thyroid lobe, and color Doppler showed diffusely increased vascularization. Its dimensions were 14x12x7 mm and volume of 0.6 mL (Figs 2 a, b). It was considered to be a recurrent PTC or PAD. Whole-body scintigraphy was without a conclusive pathological accumulation of radioiodine and the laboratory findings were negative for thyroglobulin. Additional laboratory analysis confirmed PHPT: hypercalcemia, s-Ca 2.71 mmol/L (normal: 2.06-2.60 mmol/L) and high levels of parathyroid hormone, s-PTH 170 ng/L (normal: 12-65 ng/L) and normal levels of alkaline phosphatase, s-ALP 1.48 $\mu\text{kat/L}$ (normal: 0.67-2.15 $\mu\text{kat/L}$). A subsequent parathyroid scintigraphy using a complex one-day protocol combining subtraction scintigraphy ($^{99\text{m}}\text{Tc-MIBI}$ and $^{99\text{m}}\text{TcO}_4$) with two-phase $^{99\text{m}}\text{Tc-MIBI}$ scintigraphy including SPECT confirmed the presence of PAD (Fig. 3a). Because of patient's asymptomatic form of PHPT, without renal impairment, no history of bone fracture or gastrointestinal complications, there was no reason for a rapid and radical solution. In the given situation, where the surgical criteria were not met and in particular with regard to the patient's age, only follow-up with regular monitoring of laboratory s-Ca and s-PHT would be sufficient. But prospectively the patient would still be at risk of PHPT progression and subsequent need for surgery. The patient was mentally and physically very vital for his age. From the oncological point of view PTC was described as a disease in remission. As at our endocrinology

Figure 2. US findings before PEIT, status post thyroidectomy, PAD identified in the left jugular region, volume of 0.5 mL: 2a - hypoechoic PAD, transversally, 2b - longitudinally.

Figure 3. Scintigraphy with ^{99m}Tc -MIBI: 3a – radioisotope uptake in PAD in the left jugular region before PEIT, 3b - 12 months after PEIT without uptake of the radioisotope.

Figure 4. US findings 12 months after PEIT, PAD identified in the left jugular region, volume of 0.1 mL: 4a – shrunken PAD with fibrosis, transversally, 4b – longitudinally.

outpatient clinic we perform PEIT of thyroid cysts a PAD, after consulting an endocrinologist and a nuclear medicine physician. We decided to offer this method as the most appropriate treatment option, also avoiding further surgery in the area with a history of previous surgical procedure. Patient accepted our offer the US-guided PEIT.

Within 2 months, a total of three US-guided PEIT procedures were performed according to the following scheme: first PEIT with 0.3 mL of 96% ethanol, after 14 days the second PEIT with 0.3 mL of 96% ethanol and after a month the third PEIT procedure with 0.2 mL of 96% ethanol. After the first PEIT, the laboratory findings were s-Ca 2.51 mmol/L and s-PTH

109 ng/L and after the second PEIT were s-Ca 2.29 mmol/L and s-PTH 99 ng/L. Already after the second PEIT, the laboratory values were quite favorable, since there was normocalcaemia but with still slightly increased levels of s-PTH. The US examination showed that the volume of PAD was 0.3 mL, with signs of fibrosis in the center and only traces of vascularization in the periphery of the adenoma. Therefore, the patient underwent also the third PEIT procedure.

One month after the third and last PEIT the laboratory values were s-Ca 2.20 mmol/L and s-PTH 89 ng/L, half a year after the procedures were s-Ca 2.26 mmol/L and s-PTH 64 ng/L. A year after completion of the PEIT therapy, laboratory values remained

favorable, with s-Ca 2.13 mmol/L, s-PTH 62 ng/L and s-ALP 0.92 μ kat/L. US examination one month after third PEIT showed shrunken and fibrotic PAd with volume of 0.1 mL and no signs of vascularization. The same US findings were observed at 3, 6 and 12 months (Figs 4 a, b). A control scintigraphy of the parathyroid gland a year after the PEIT was negative (Fig. 3b).

All three US-guided PEIT were performed on an outpatient basis; the patient tolerated the procedure very well. There were no subsequent local complications and the desired objective was achieved.

DISCUSSION

The primary therapeutic method in the management of PHPT is surgical treatment - parathyroidectomy. It is indicated in all symptomatic patients. In asymptomatic patients the NIH recommendations from 2002 are applied, parathyroidectomy is indicated in patients meeting the following criteria: s-Ca increase by 0.25 mmol/L above the norm, calciuria exceeding 10 mmol/24h, decrease in creatinine clearance of 30%, and advanced osteoporosis with the T-score less than -2.5 SD in any location and age below 50 years (8). The workshop held in 2009 further modified these criteria - calciuria without nephrolithiasis is not an indication for parathyroidectomy (9).

In the United States, about 40-50% of patients with mild asymptomatic PHPT do not meet these criteria. Their 10-year follow-up (non-specific pharmacotherapy) showed that 25% of them developed symptomatic disease, and fulfilled the criteria for parathyroidectomy, in other patients the laboratory values and bone mineral density remained unchanged (2).

Experiences with US-guided PEIT in the treatment of PHPT were published either in the form of case reports, or small clinical sets. The clinical sets, however not large enough for broader statistical conclusions rather demonstrate greater experience of the respective clinic with the use of this method. Nevertheless this information can be further used as guidance for incorporation of this method into the treatment plans for less experienced clinics.

The clinical sets include dozens of patients and their success rate ranges between 33-89%. In addition, the sets differ in the dose of applied 96% ethanol and dosing interval as well as the follow-up period. Danish physician Karstrup was the first one to investigate the therapy on a larger scale. In 1989 he treated 20 patients with a success rate of 44% and then in 1993 two sets,

the first of 18 patients with a success rate of 56%, and second of 14 patients with a success rate of 79%, the sets differed as for the interval between applications - one month vs. one week (4, 10). The report on the largest set and in great detail was published in 1998 by Harman; it included 36 patients treated at the Mayo Clinic in the period 1987-1998. Sustained therapeutic success was achieved in 33% of patients and transient normocalcaemia was reported in 47% of patients. When analyzing the causes of PEIT method failure, he identified the following causes: ethanol was not injected into hyperfunctional PAd but rather to a thyroid nodule, PHPT was caused by a multiglandular disease of the parathyroid glands (hyperplasia of all four glands or there was an additional PAd), or the proper PAd was treated, but the dose of applied ethanol was insufficient (11). In 1998, French authors published a set of 27 patients with a success rate of 58% (12). The last published set was published in 2008 in Greece, where Stratigis treated 19 patients with a high success rate of 89% (13).

These not numerous clinical sets unfortunately do not allow for broader statistical conclusions and recommendations, as stated above. Substantial shared information from all of these reports is that there was not reported any severe, life-threatening complication of the method. A typical adverse effect of the PEIT is mild local pain lasting for 24 to 48 hours after administration of ethanol. Additionally, a small hematoma can develop. Less often adverse effect is dysphonia or vocal cord paresis, usually transient. If the method fails and surgery - parathyroidectomy is ultimately required, histology usually describes periglandular tissue fibrosis, likely caused by a "leak" of the applied ethanol. This of course complicates the surgical procedure itself (4).

Description of the PEIT technique according Harman: The patient lies on back with head slightly tilted back. The procedure is performed under sterile conditions. Some authors use local anesthesia. Puncture technique is performed using "free hand" technique under US guidance. The tip of the needle must be well detected in the PAd, and then the application of ethanol is performed slowly. A hyperechoic "jet" spreading in all directions of the adenoma appears on the screen. When the application is too fast, this "jet" may worsen the visualization of the PAd. Therefore, slow application of ethanol in small doses into multiple sites of adenoma is important. The dosage for one application is between 50-70% of the PAd volume (11). Stratigis applied a dose corresponding to 85% of the PAd volume (13).

There is no uniform time schedule for PEIT applications. Intervals between laboratory and US controls and possible additional ethanol application vary. For example Harman and Cercueil chose an application interval of 24 hours, Stratigis 2 weeks, and Karstrup one week or one month (4, 11-13). If the control laboratory results reveal elevated levels of s-Ca and s-PTH, PEIT is administered repeatedly until normal levels are achieved. Doppler US detects area with the greatest blood supply and the dose of ethanol is administered into the very spot (11). In our patient, we performed the first two PEIT at a 14-day interval and the third PEIT with a lower dose of ethanol after 1 month. The amount of 96% ethanol administered in one dose was equivalent to 50% of the current volume of PAd.

Coincidence of thyroid disease and PHPT was described in the past, but it is rather scarce. For example, Wagner's set from 1999 including 13,000 patients with thyroid disease showed incidence of PHPT of 0.3% or Morita's set from 2008 including 326 patients showed PHPT incidence of 3.1% (14, 15). According to the literature overview, in the surgical sets of patients with PHPT (hundreds of patients), the incidence of thyroid cancer varies between 2.1 to 17.6%. In the two largest sets of patients, Linos from 1982 including 2,058 PHPT patients operated on for thyroid carcinoma showed incidence of 2.5% and Milas from 2005 including 1,195 patients showed incidence of 4.6% (16, 17). Often they found a carcinoma that had not been known before the surgery and was diagnosed only histologically in a simultaneously removed nodal goiter. In 2008 Morita in his set of patients compared the incidence of PHPT in patients with primary disease of the thyroid gland and the incidence of thyroid carcinoma in patients primarily indicated for parathyroidectomy. In the set of 200 patients with PHPT a preoperative US examination revealed a contaminant nodule in the thyroid gland in 102 patients (51%). Forty patients simultaneously underwent thyroidectomy and parathyroidectomy; in 12 (6%) of them, histology identified papillary or follicular carcinoma with average size of 5 mm (carcinomas in situ). However, preoperatively performed fine-needle aspiration biopsy (FNAB) (44 patients) showed malignant cytological findings only in one patient, in 6 patients the findings were of uncertain significance (15). According to the data of Globocan (Incidence of Malignant Diseases Worldwide, 2012) thyroid carcinoma accounted for 2.1% of all new cancer cases, about 0.9% in men and 3.4% in women. In Europe these carcinomas accounted

for 1.7% of cases of new malignant tumors, 0.7% in men and 2.8% in women. They are the most common malignancy of the endocrine system and held the 16th position worldwide and the 18th position in Europe in the incidence of malignant diseases (18).

It is questionable whether to perform FNAB of PAd to exclude potential parathyroid carcinoma (PCa) for each patient indicated for PEIT. PCa is rare diagnosis and may be suspected based on significance of clinical signs of PHPT, size of the parathyroid gland, and laboratory findings. PHPT due to a PAd is usually characterized by mild symptoms and course of the disease; on the contrary, clinical signs and laboratory findings of PCa are usually eminent. In PCa, serum PTH levels are 3 to 10 times higher than normal, which is in contrast to the average 2-fold increase seen in PAd. As for serum calcium levels, these often range from 3.5 to 3.75 mmol/L in PCa but are not that high in PAd, usually increased only by 0.25 to 0.5 mmol/L above the normal (19).

The US findings typical for PAd are as follows: a solid, homogeneous, hypoechoic mass, with an average size of 16-19 mm (range 4-63 mm) and hypervascularization confirmed by Doppler paging. The shape is oval, ellipsoidal, or bean-like (20, 21). US scan of PCa may be distinguished from PAd by its size, usually above 3cm, nonhomogeneous structure, frequent degenerative changes - pseudocystic cavities, calcifications and irregular borders. The echogenicity of PCa could be hyper and also hypoechoic, depending on the presence of areas of bleeding or necrosis. However rarely seen, large degenerated PAd may also be of hyperechoic US image, thus in these cases FNAB is recommended. In transverse US scan the most of PCa have ratio depth/width ≥ 1 and on the contrary a ratio < 1 is characteristic of PAd (22).

According to Cercueil *et al.* FNAB does not provide significant improvement on the results of PEIT treatment and abandoned it, however Tc-MIBI scintigraphy may be useful in difficult patients (12).

We believe that in the case of US image of small and typical PAd FNAB is unnecessary. We perform it only in patients with US image of large or atypical PAd, or in the case of suspected parathyroid cyst, then investigation of PTH levels in punctuate is helpful to confirm the diagnosis (23, 24). ^{99m}Tc -MIBI is always performed before PEIT to confirm the localization of the PAd found on US, and also after the treatment in order to confirm its results.

Our case report showed importance of combining imaging methods in the postoperative

monitoring of patients after thyroidectomy for PTC. Negative laboratory level of thyroglobulin and negative control scintigraphy of the thyroid gland are not sufficient. US can detect additional affection in this area, as in our case PAd.

In conclusion, well indicated patients can benefit from using US-guided PEIT as an alternative procedure in the management of PHPT, especially polymorbid elderly patients or those with increased surgical risk. And also the patients with previous history of neck surgery can benefit from the method.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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