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CLINICAL MANAGEMENT OF ENDOCRINE DISEASES

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Medullary thyroid carcinoma treated with percutaneous ultrasound-guided radiofrequency ablation

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Abstract

Purpose Minimally invasive image-guided thermal ablation has been proposed as alternative to surgery for treatment of benign thyroid nodules and recurrent differentiated thyroid carcinoma. Here, we report for the first time the use of radiofrequency ablation (RFA) in a patient with non-metastatic medullary thyroid carcinoma (MTC) who did not undergo surgery due to high anesthesiological risk.

Methods and results A 64-year-old woman was referred to our institution for a routine endocrinological visit. No thyroid-related symptoms were present. She had a history of metabolic, cardiovascular and neurological diseases. On clinical examination, a nodular lesion of about 10 mm was palpable in the right thyroid lobe; ultrasonography (US) confirmed the presence of a 13 mm thyroid nodule in the lower pole of the right lobe, that was hypoechoic and with regular margins. Serum calcitonin (Ctn) level was significantly high (647 pg/mL). Fine-needle aspiration (FNA) of the thyroid nodule was negative for malignant cells, but the marked increase of Ctn level in the FNA wash-out fluid confirmed the diagnostic suspicion of MTC. Since patient refused surgery due to high anesthesiological risk, percutaneous US-guided RFA in single session was performed. At 6-months follow-up the serum Ctn level decreased from the initial value of 647 pg/mL, reaching near-normal range (15 pg/mL), and neck ultrasound showed a complete necrosis of the tumour. Afterward, serum Ctn slowly increased to 49 pg/mL at 15-month follow-up. The US performed at 6 and 12 months of follow-up revealed fibrotic tissue in place of the thyroid nodule, without evidence of cervical lymph-node metastases.

Conclusions This clinical case suggests that RFA may be effective and safe for treatment of MTC when surgery cannot be performed.

Keywords Medullary thyroid carcinoma · Radiofrequency ablation · Calcitonin · Ultrasound

Introduction

Medullary thyroid carcinoma (MTC) accounts for ~1–5% of all thyroid malignancies and can occur either as sporadic (85% of cases) or hereditary form (the remaining 15% of cases) [1]. MTC originate from the neural crest-derived C-cells, and its clinical behaviour can range from indolent to highly aggressive and progressive disease characterised by early lymph nodal metastases [2]. The survival rate of MTC is comparatively lower as compared to well-differentiated thyroid tumours of follicular-cell origin [2].

Therapeutic strategies for MTC treatment are fewer than those for well-differentiated thyroid carcinomas. Total thyroidectomy, with or without compartment-oriented lymph node dissections, is the only therapeutic approach with a potential curative intent for localised or locally advanced MTC [1]. However, systemic therapy with tyrosine kinases inhibitors has a role only in patients with advanced and progressive disease [3].

Image-guided tumour ablation has become a well-established hallmark of local cancer therapy [4–6]. Specifically, radiofrequency ablation (RFA) has been proposed as a valid alternative to surgery for benign thyroid nodules

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[7–12] and recurrent differentiated thyroid carcinoma [7, 13, 14]. To our best knowledge, no cases have been so far published demonstrating the effectiveness and safety of RFA in MTC.

We hereby describe the outcome of MTC treated by RFA in a patient who did not undergo surgery due to high anesthesiological risk.

Patient

A 64-year-old female patient was referred to our Institute for a routine endocrinological evaluation. She had a history of atrial fibrillation, dilatative cardiopathy with low ejection fraction (EF < 35%), left hemispheric ischemic stroke, type 2 diabetes mellitus and chronic renal insufficiency. Moreover, she underwent endarterectomy for critical stenosis of the left internal carotid artery. She was on therapy with warfarin, furosemide, spironolactone, bisoprolol, metformin and allopurinol.

Neither history of thyroid disease or radiation therapy in her cervical region, nor thyroid-related symptoms were reported. On clinical examination, a nodular lesion of about 10 mm was palpable in the right thyroid lobe without cervical lymphadenopathy. The serum thyrotropin (TSH) level was 6.04 mU/L (reference range 0.5–4.5) and the free thyroid hormones were in the normal range (free T4 was 12 pmol/L and free T3 was 4 pmol/L), while the thyroid autoantibodies were positive, indicating autoimmune subclinical hypothyroidism. Neck sonography (US) revealed, in the lower pole of the right lobe of the thyroid gland, a 13 × 8 mm hypoechoic nodule with regular margins, posteriorly located, just adjacent to the laryngeal recurrent nerve course (Fig. 1). On both colour Doppler and microvascular imaging the nodule showed only mild, mostly peripherally located vascularity, while on contrast-enhanced ultrasound (CEUS) (intravenous injection of 4.8 mL of sulphur hexafluoride) (SonoVue, Bracco, Milan, Italy) it appeared slightly hypovascular compared to the perilesional thyroid parenchyma both on arterial and venous phase. No abnormalities suggesting possible malignancy were found in the laterocervical and central lymph node compartments.

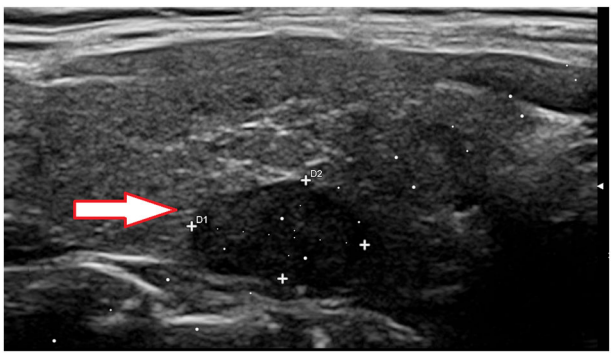

Fig. 1 Ultrasound features of medullary thyroid carcinoma (arrow) before radiofrequency ablation

Serum calcitonin (Ctn) values resulted to be high (647 pg/mL, normal value: <10 pg/mL) consistent with diagnosis of MTC. Therefore, an US-guided percutaneous fine-needle aspiration (FNA) of thyroid nodule was performed. The cytological result was negative for thyroid cancer (THYR2) according to the Bethesda System for Reporting Thyroid Cytopathology [15], but Ctn levels in the FNA wash-out fluid was found to be remarkably increased (>2000 pg/mL), thus confirming the biochemical suspicion of MTC. According with ATA guidelines based on very high serum Ctn levels [1], a total-body computed tomography was performed resulting negative for distant metastases.

The possible coexistence of pheochromocytoma was excluded by measurement of plasma and urinary metanephrine levels, both of them resulting in the normal range.

Because of high anesthesiological risk related to multiple comorbidities, the patient refused surgical treatment and RFA was chosen as alternative therapeutic approach.

Mild sedation with paracetamol (Angelini, Ancona, Italy) (1 g), ketorolac tromethamine (Recordati, Milan, Italy) (10 mg), ondansetron-teva (Novartis Farma, Origgio, Italy) (4 mg) and midazolam chloridrate (Hameln Pharma Gmbh, Germany) (1 mg) and local anesthesia with injection of 2–5 mg of 2% lidocaine were preliminarly performed. Under real-time US guidance (MyLab 9, Esaote, Genoa, Italy) with a 7–15 MHz linear transducer provided with biopsy guidance device (Civco, Kalona, Iowa, USA), a 16 G RF electrode with 0.7 cm exposed tip, connected to a hybrid radiofrequency/microwaves (MWA) generator (Amica HS, HS Hospital Service, Aprilia, Italy) was inserted into the nodule, using the "moving shot" technique [10]. This approach allows to decrease thermal injury to the lowest level, sparing critical cervical structures, such as the recurrent laryngeal nerve, and to make the isthmic parenchyma act as a buffer between the target nodule and the RF electrode insertion site, preventing the formation of painful hematomas. Using only one skin entry point and changing only the needle angulation, three subsequent insertions were performed. The electrode was always pulled back and repositioned when the impedance level exceeded the initial level of 50 Ohms and an acoustic signal was emitted by the machine. For each insertion, 30-W power energy was deposited. The procedure was stopped when the whole nodule was filled with gas produced by the ablation. Total treatment time and total amount of energy deposited were 214 s and 4.1 kJ, respectively. No procedure-related complications were detected, and the patient was discharged 2 h after the end of the procedure.

The thyroid function was within the normal range (TSH serum level 2.71 mU/L, normal range: 0.25–4.2) in the post-procedural period; the subclinical hypothyroidism recognised at the first clinical evaluation, was not observed anymore during the follow-up.

After RFA, serum Ctn level and carcinoembryonic antigen (CEA) were measured every 3 months and thyroid US and CEUS were performed at 1, 6, and 12-months. Within the first 6-months, the serum Ctn levels significantly decreased to 15 pg/mL. Afterward, serum Ctn levels increased slowly reaching 49 pg/mL at 15-month follow-up. Likewise, CEA level had upward trend, with a value of 4.3 ng/mL (normal values < 10 ng/mL) at 12 months and 5.5 ng/mL at 15 months.

On sonographic assessments at 1 and 6 months the nodule showed a slight increase of echogenicity due to initial fibrotic changes, with complete lack of blood flow signals on colour and power Doppler. In addition, on CEUS complete avascularity due to coagulative necrosis was found. In contrast with initial biochemical relapse of disease, the neck sonography at 12-months detected a triangular 7 mm hypoechoic tissue due to fibrotic tissue without blood flow signals on microvascular imaging (Fig. 2). On CEUS complete avascularity of this solid, fibrotic area was confirmed both in arterial and portal phase.

Discussion

In this paper, we describe for the first time the effective use of RFA for treatment of early MTC in a patient who did not undergo surgery due to high anaesthesiologic risk.

The action of RFA, clinically employed since the 90's for the local treatment of neoplastic diseases (of liver, kidney, lung, bone, etc.), is based on the frictional heat generation due to local tissue resistance to electrical current moving from the electrode applicator to the remote grounding pad. The temperature rise inside the target crossed by the electrode creates vaporisation, coagulation (that overcomes the tumour margins forming a perilesional ablative halo), tumoral dehydration and finally shrinking of the target.

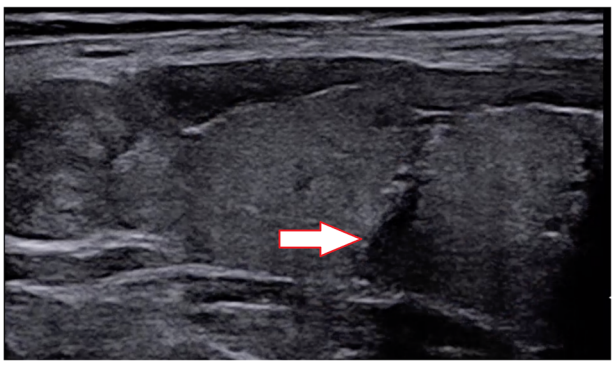

Fig. 2 Ultrasound features of medullary thyroid carcinoma (arrow) 12 months after radiofrequency ablation

Over the last two decades, minimally invasive US-guided RFA has been proposed for the treatment of benign non-functioning thyroid nodules either causing early local discomfort or large nodules in patients presenting with local symptoms or cosmetic complaints when surgery is contra-indicated or declined [7, 8, 10, 11, 16, 17]. In addition, RFA is also indicated for autonomously functioning nodules hot/warm on scintiscan, either toxic or pretoxic, when surgery and radioiodine cannot be performed [9, 18, 19]. For both indications, RFA, mostly performed with transisthmic approach and moving shot technique has the main role to coagulate the nodule, leaving a thin peripheral halo of safe tissue at the periphery, in order to preserve the capsule and the perilesional tissue. After reabsorption of the necrotic tissue, a significant nodule shrinkage, ranging from 75 to 93% of the initial volume [10–12, 16, 20], substantially stable for years after RFA, coupled with marked clinical improvement in nodule-related symptoms has been reported in the literature. Remarkably, thyroid function is not affected by RFA, and this is an important advantage as compared with surgery or radioiodine therapy. The major complication rate is significantly low, around 1.4% [21]. Major complications reported include nerve injuries (recurrent laryngeal nerve, cervical sympathetic ganglion, brachial plexus and spinal accessory nerve), nodule rupture and permanent hypothyroidism. There are no reported life threating complications.

RFA (and laser in some series) has been used to treat metastatic lymph nodes from recurrent papillary thyroid carcinoma, in patients at surgical risk, when radioiodine is not effective [13, 14, 22], with resulting marked shrinkage of adenopathies, coupled with serum thyroglobulin reduction. In addition, recently MWA and laser ablation have been proposed for the treatment of papillary thyroid carcinomas with a maximum diameter <10 mm, without cervical lymph node metastasis, in patients either reluctant to undergo surgery or inoperable [23, 24]. Complete reabsorption of the nodule was reported in over 85% of the cases on follow-ups ranging from 12 to 36 months after ablation. In all these cases of neoplastic diseases, both primary and nodal, the aim of ablation is the complete treatment of the whole lesion.

No cases of thermal ablation of primary MTCs have, to date, been reported in the literature, to our knowledge. In our patient with MTC, using three transisthmic insertions of a RF electrode with moving shot technique, the tumour was completely ablated, as suggested by the follow-up sonography evaluations. Particularly, after 12-month follow-up, the B-mode, colour Doppler, microvascular imaging and

CEUS revealed a very small (7 mm), triangular-shaped, fibrotic area, positioned where the tumour was located, completely avascular during the whole study. These morphological changes of the tumour were accompanied by a clinically significant decrease in serum Ctn values. This clinical case confirms that Ctn is the mainstay in diagnosis of MTC and provides a further evidence to support the use of Ctn assay in the diagnostic work-up of thyroid nodules [25–27]. In fact, our patient had higher Ctn in both peripheral blood and in thyroid nodule FNA was-out fluid, notwithstanding the negative cytological result [28] and the low-intermediate suspicion features at the US evaluation [29]. During the 15-month follow-up after RFA procedure, serum Ctn decreased but not normalised suggesting that MTC may not be cured. This outcome was not completely unexpected, since our patient had a MTC >10 mm and basal Ctn values higher than 500 pg/mL. In these cases, previous experiences reported high risk of multifocality and lymph node metastases [1]. Based on this risk, a strict ultrasonography and biochemical follow-up is needed in order to early recognise recurrences/metastases of MTC. In these cases, RFA may be re-proposed as alternative to surgery, such as performed for other neoplastic diseases.

In conclusion, our case report suggests that RFA may be considered as a safe and effective therapeutic tool for MTC that cannot be surgically operated due to high anesthesiological risk. Further controlled-studies are needed to validate RFA's role in the management of MTC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving a human participant were in accordance with the ethical standards of the Humanitas Ethical Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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