CLINICAL STUDY

The usefulness of ^{99m}Tc -sestaMIBI thyroid scan in the differential diagnosis and management of amiodarone-induced thyrotoxicosis

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Abstract

Background: Amiodarone-induced thyrotoxicosis (AIT) is caused by excessive hormone synthesis and release (AIT I) or a destructive process (AIT II). This differentiation has important therapeutic implications.

Purpose: To evaluate ^{99m}Tc -sestaMIBI (MIBI) thyroid scintigraphy in addition to other diagnostic tools in the diagnosis and management of AIT.

Subjects and methods: Thyroid $^{99m}\text{TcO}_4^-$ and ^{99m}Tc -MIBI scintigraphies were performed in 20 consecutive AIT patients, along with a series of biochemical and instrumental investigations (measurement of thyrotrophin, free thyroid hormones and thyroid autoantibodies; thyroid colour-flow Doppler sonography (CFDS) and thyroid radioiodine uptake (RAIU)).

Results: On the basis of instrumental and laboratory data (excluding thyroid ^{99m}Tc -MIBI scintigraphy) and follow-up, AIT patients could be subdivided into six with AIT I, ten with AIT II and four with indefinite forms of AIT (AIT Ind). ^{99m}Tc -MIBI uptake results were normal/increased in all the six patients with AIT I and absent in all the ten patients with AIT II. The remaining four patients with AIT Ind showed low, patchy and persistent uptake in two cases and in the other two evident MIBI uptake followed by a rapid washout. MIBI scintigraphy was superior to all other diagnostic tools, including CFDS (suggestive of AIT I in three patients with AIT II and of AIT II in three with AIT Ind) and RAIU, which was measurable in all patients with AIT I, and also in four out of the ten with AIT II.

Conclusion: Thyroid MIBI scintigraphy may be proposed as an easy and highly effective tool for the differential diagnosis of different forms of AIT.

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Introduction

Amiodarone is an iodine-rich drug effective in the treatment of tachyarrhythmias and coronary heart disease (1, 2). This drug may cause several side effects including overt hypothyroidism (amiodarone-induced hypothyroidism) and hyperthyroidism (amiodarone-induced thyrotoxicosis, AIT) (3–7).

AIT may be caused by an excessive thyroïdal hormone synthesis and release induced by the iodine load in patients with underlying thyroid autonomy (nodular or diffuse goitre, or latent Graves' disease; type 1 AIT, AIT I), or be the consequence of a destructive process in patients with normal thyroid gland (type 2 AIT, AIT II) (8–11), although indefinite forms (AIT Ind) may also occur (7).

The differentiation between AIT I and AIT II is an important prerequisite for the correct therapeutic choice (9, 12) and is based on clinical, biochemical and imaging results. Typical AIT I is characterized by diffuse or nodular goitre with or without serological or

sonographic evidence of thyroid autoimmunity, increased thyroid blood flow at colour-flow Doppler sonography (CFDS) and measurable 24-h thyroid radioiodine uptake (RAIU) (7, 11–17). On the other hand, normal or slightly enlarged thyroid gland without significant blood flow at CFDS, high serum interleukin-6 concentrations and undetectable RAIU is frequently observed in AIT II (7, 11–17). The differential diagnosis between AIT I and AIT II remains difficult since misleading results may be observed with each of the proposed diagnostic tools, and long-term follow-up including the response to different therapeutic protocols may be needed for the final diagnosis.

^{99m}Tc -sestaMIBI (MIBI) is a well-known lipophilic monovalent cation that shows an increased uptake in epithelial cells containing high numbers of mitochondria (18–20). For this reason, increased retention of MIBI is currently employed to detect hyperfunctioning parathyroid tissue (21, 22) and may be observed in benign or malignant thyroid tumours, especially of oncocyctic nature

(23). Increased MIBI retention has also been described in hyperfunctioning thyroid tissue (toxic adenoma or toxic diffuse goitre) (24, 25) and this phenomenon is believed to be the consequence of increased mitochondria number in hypermetabolic cells (26, 27). On the other hand, MIBI accumulation is reduced or absent in apoptotic or necrotic processes involving mitochondrial membrane potential collapse (28, 29).

Starting from the above considerations, we wondered whether MIBI thyroid scintigraphy could be employed in the diagnostic evaluation of AIT. To this purpose, thyroid MIBI scintigraphy has been performed in 20 consecutive patients with different types of AIT.

Patients and methods

Patients

We evaluated 20 consecutive patients with AIT on long-term therapy with amiodarone (200–400 mg daily) for atrial fibrillation or flutter. All patients were examined in the Endocrinology Unit and referred for routine evaluation to the Sonography and Nuclear Medicine Units of our institution over a 3-year period (January 2005–January 2008). At the time of diagnosis, all patients were receiving the drug, which was immediately withdrawn. AIT developed from 45 days to 4 years after institution of amiodarone therapy.

In all patients urinary iodine excretion, serum-free thyroxine (fT_4), free tri-iodothyronine (fT_3), thyroid-stimulating hormone (TSH), anti-thyroglobulin (AbTg), anti-thyroid peroxidase (AbTPO) and anti-TSH receptor autoantibodies (TRAb) were determined as detailed below. Patients were also submitted to clinical and instrumental examination including CFDS, RAIU, $^{99m}TcO_4^-$ and MIBI scintigraphy.

All patients gave their written informed consent to all the proposed diagnostic procedures. Diagnosis of AIT was confirmed in all cases by increased serum fT_4 and fT_3 concentrations, associated with undetectable or very low (<0.05 mU/l) serum TSH levels. A tentative diagnosis of AIT I was made in the presence of at least two of the following conditions: the presence of diffuse goitre associated with positive anti-thyroid autoantibodies (ATAs); nodular goitre; normal or increased thyroid blood flow; measurable ($>1\%$) RAIU and detectable uptake at $^{99m}TcO_4^-$ thyroid scintigraphy. In the presence of normal or slightly enlarged thyroid gland, low blood flow by CFDS, undetectable ($<1\%$) RAIU and no $^{99m}TcO_4^-$ thyroid scintigraphy image, the patient was assumed to be affected by AIT II. The definitive diagnosis was established on the basis of clinical outcome observed during the follow-up.

Demographic data, cumulative amiodarone dose, initial diagnosis, biochemical and imaging studies (CFDS, RAIU, Thyroid $^{99m}TcO_4^-$ and MIBI scintigraphies), therapy, time elapsed to reach euthyroidism

and final diagnosis of the patients studied are reported in Table 1.

All patients with initial diagnosis suggestive of AIT I were treated with methimazole (MMI) 40 mg daily associated with $KClO_4$ (1 g daily for a maximum of 45 days, then the treatment was continued with MMI alone (30)), while patients with initial diagnosis suggestive of AIT II were treated with 30–40 mg/day prednisone which was then gradually tapered. These therapeutic approaches were effective in 16 patients, while the remaining four patients (nos 7–10) needed combined therapy (MMI plus $KClO_4$ and prednisone) and were therefore considered affected by AIT Ind. In particular, nos 7 and 8 patients, initially classified as affected by AIT I for the presence of positive TgAb (42.9 U/ml), small vascularized nodular goitre and detectable RAIU (patient no. 7) and positive TRAb (6.76 U/ml) and detectable RAIU (patient no. 8), both required addition of prednisone to MMI and $KClO_4$; nos 9 and 10 patients, initially classified as affected by AIT II for absent thyroid blood flow at CFDS, both required addition of MMI and $KClO_4$ to reach the euthyroid state.

Assays

TSH, fT_4 , fT_3 , AbTPO and AbTg were measured by automatic ultrasensitive chemiluminescence assays (Ortho Clinical Diagnostic Sp, Milan, Italy, for fT_3 , fT_4 and TSH, Immulite 2000; Diagnostic Products Corporation, Los Angeles, CA, USA; distributor Medical Systems Corporation, Genoa, Italy, for anti-TPOAb and anti-TgAb), and TRAb by radioreceptor assay (TRA-Khuman, BRAHMS, Henningsdorf, Germany; distributor DASIT SpA, Milan, Italy). Normal values were: fT_4 , 7.7–21.9 pg/ml; fT_3 , 2.7–5.27 pg/ml; TSH, 0.2–3.0 μ U/ml; TgAb, <40 U/ml; TPOAb, <35 U/ml and TRAb, <1.0 U/ml.

Thyroid ultrasound and CFDS

Thyroid ultrasound and CFDS were performed using a Sequoia 512 colour Doppler system (Acuson Co., Mountain View, CA, USA) with an 8 MHz linear electronic transducer and 7 MHz colour Doppler frequency. Longitudinal and transversal scanning were performed. Thyroid volume, parenchymal echogenicity and the presence of nodules were assessed. Thyroid volume was calculated by the ellipsoid method, as described elsewhere (23). The CFDS aspects of thyroid parenchyma (P) were described separately from those of the nodules (N) and classified as already reported (6). Briefly, CFDS patterns of the thyroid parenchyma (P) were classified as: P0 (absence of blood flow); P1 (minimal parenchymal blood flow); P2 (mild increase of parenchymal blood flow); P3 (marked increase of parenchymal blood flow). CFDS patterns of thyroid nodules (N) were classified as: N0 (absence of nodules), N1 (absence of peri- and intranodular blood flow), N2

Table 1 Clinical features, instrumental data of 20 patients with amiodarone-induced thyrotoxicosis (AIT).

Patients numbers	Age (years)	Sex	AM (g)	TSH (μ U/ml)	fT ₄ (pg/ml)	fT ₃ (pg/ml)	AbTg (IU/ml)	AbTPO (IU/ml)	TRAb (U/ml)	Vol (ml)	CFDS	RAIU (%)	^{99m} Tc Scint	MIBI Scint	Initial AIT diagnosis	Final AIT diagnosis	Therapy		Outcome Tot (comb) days
																	MMI KClO ₄	Pd	
1	84	F	140	0.001	69.9	13.2	<20	<10	4.06	39.5	P1/N2	1	—	+	AIT I	AIT I	+	=	90
2	34	F	144	0.001	50	6.2	<20	<10	0.20	35	P1/N1	1	—	+	AIT I	AIT I	+	=	120
3	81	F	16	0.004	39	3.9	<20	<10	0.32	34	P1/N1	3	—	+	AIT I	AIT I	+	=	60
4	17	F	142	0.001	45	7.0	<20	<10	0.41	38	P1/N1	1	—	+	AIT I	AIT I	+	=	90
5	66	F	140	0.001	39	7.1	<20	<10	0.27	32	P1/N1	2	—	+	AIT I	AIT I	+	=	90
6	48	F	280	0.001	17.6	7.3	<20	<10	0.34	26.2	P0/N1	8	+	+	AIT I	AIT I	+	=	30
7	54	M	140	0.02	63.6	15.6	42.9	14.5	0.21	21.7	P1/N1	2	—	Low	AIT I	AIT Ind	+	+	75 (30) ^a
8	49	M	34	0.001	33	5	<20	<10	6.76	26	P0/N0	3	—	+(w)	AIT I	AIT Ind	+	+	52 (7) ^a
9	67	M	142	0.005	60	8.7	<20	10	0.37	18	P0/N0	0	—	+(w)	AIT II	AIT Ind	+	+	50 (30) ^a
10	54	M	70	0.001	64	12	<20	<10	0.30	40	P0/N0	1	—	Low	AIT II	AIT Ind	+	+	60 (30) ^a
11	52	M	140	0.001	26.7	7.2	<20	<10	0.27	23	P0/N0	1	—	—	AIT II	AIT II	=	+	7
12	71	M	210	0.01	26	6.8	<20	11	0.30	21.5	P0/N0	1	—	—	AIT II	AIT II	=	+	10
13	56	M	210	<0.001	61.7	13.9	<20	26	0.41	16.3	P0/N0	0	—	—	AIT II	AIT II	=	+	60
14	64	M	140	<0.001	41.4	6.9	<20	<10	0.34	12	P0/N0	0	—	—	AIT II	AIT II	=	+	50
15	71	M	210	0.003	30.3	4	<20	<10	0.30	11	P0/N0	0	—	—	AIT II	AIT II	=	+	7
16	59	M	210	0.047	28.2	5.9	<20	19.3	0.36	22.9	P0/N0	1	—	—	AIT II	AIT II	=	+	7
17	75	M	140	0.001	44	7.5	<20	<10	0.77	14.7	P1/N0	0	—	—	AIT II	AIT II	=	+	90
18	50	M	39	0.001	50.1	12.2	420	<10	0.30	15.7	P0/N1	0	—	—	AIT II	AIT II	=	+	14
19	75	M	560	0.001	53.7	13.2	<20	<10	0.35	32	P1/N0	1	—	—	AIT II	AIT II	=	+	60
20	76	M	140	0.001	48.2	10.2	<20	<10	0.26	25	P0/N0	0	—	—	AIT II	AIT II	=	+	60

AM, cumulative amiodarone dose; V, thyroid volume; P-CFDS, parenchyma CFDS pattern; N-CFDS, nodule CFDS pattern; RAIU, radioiodine uptake; ^{99m}Tc scint, thyroid ^{99m}TcO₄ scintigraphy; MIBI scint, ^{99m}Tc-sesta MIBI scintigraphy (w, rapid MIBI washout and Low, low MIBI uptake); Ind, indefinite; Therapy: Pd, prednisone, for other details see text.

^aNumber in parenthesis indicates the number of days on combined anti-thyroid and prednisone therapies.

(perinodular blood flow with absence of or slight intranodular vascularization) and N3 (marked intranodular blood flow).

Thyroid RAIU

Thyroid RAIU values were measured in every patient 3 and 24 h following the administration of a tracer dose (150–180 KBq) of Na- ^{131}I , using a Captus 2000 RAIU system (Campintec, New York, NY, USA). Normal-3 and 24-h RAIU values in our area, which is borderline iodine deficient (31), ranged between 5–20 and 14–40% respectively.

Thyroid $^{99\text{m}}\text{TcO}_4^-$ scintigraphy

Thyroid scintigraphy with $^{99\text{m}}\text{TcO}_4^-$ was performed by means of a computerized γ -camera equipped with a pinhole collimator (Elsint, SP4, Haifa, Israel) 10 min after i.v. injection of 110 MBq $^{99\text{m}}\text{TcO}_4^-$, with anterior, left anterior oblique and right anterior oblique projections. The scintigraphic patterns were categorized into negative (–; completely absent uptake of the radiopharmaceutical in thyroid parenchyma) and positive (+; visible uptake of the radionuclide) patterns.

Thyroid $^{99\text{m}}\text{Tc-MIBI}$ scintigraphy

Thyroid scintigraphy with $^{99\text{m}}\text{Tc-MIBI}$ (Cardiolite, Bristol-Meyers-Squibb, Brussels, Belgium) was performed by means of the same γ -camera used for $^{99\text{m}}\text{TcO}_4^-$ scintigraphy after i.v. injection of 185 MBq of MIBI without any specific preparation. Images were acquired on early and delayed times: early images, with an acquisition time of 3 min, at 2, 10 and 15 min and a late image 1 h after tracer administration.

Results

MIBI scintigraphy in AIT

As reported in Table 1, a clear MIBI diffuse retention was observed in all the six patients with AIT I, while no significant uptake was found in all patients with AIT II. As also shown in Table 1, a faint persistent MIBI uptake was found in two out of the four patients of AIT Ind, while in the other two patients MIBI uptake showed a rapid washout (within 10 min). Representative MIBI scans obtained in patients with different forms of AIT are reported in Fig. 1.

Comparison of MIBI scintigraphy with CFDS, RAIU and $^{99\text{m}}\text{TcO}_4^-$ scintigraphy in differential diagnosis of AIT

When the results obtained by all the instrumental procedures were compared (Table 1), MIBI

Figure 1 Representative images of $^{99\text{m}}\text{Tc-MIBI}$ scan of thyroid glands affected by (A) AIT I, (B) AIT Ind and (C) AIT II.

scintigraphy was found to be the single procedure able to completely differentiate AIT I from AIT II. MIBI scintigraphy was superior also to CFDS, which is believed to be a highly effective imaging procedure for AIT. Three patients with AIT II (nos 17–19) had in fact CFDS features suggestive of AIT I and three patients with AIT Ind (nos 8–10) had CFDS features suggestive of AIT II. As expected, thyroid RAIU <1% and ^{99m}Tc scintigraphy were not able to effectively discriminate different forms of AIT.

Discussion

This study provides clear evidence that MIBI scintigraphy can be employed to differentiate AIT I from AIT II cases. Positive MIBI uptake was in fact detected in all patients with a final diagnosis of AIT I or AIT Ind, while it was absent in all patients affected by AIT II. The finding of positive MIBI scintigraphy in AIT I is in keeping with previous studies showing increased MIBI retention in hyperfunctioning thyroid tissue (24–26). On the other hand, negative MIBI uptake in AIT II is consistent with the presumptive destructive nature of this condition, suggested both by *in vitro* and *in vivo* studies. In fact, the collapse of plasmatic and mitochondrial membrane potential occurring in apoptotic and necrotic cells leads to reduced/prevented MIBI accumulation (28, 29). A direct cytolytic effect of amiodarone on cultured thyroid follicular cells has been well documented (11, 32) and the histological examination of some patients with AIT submitted to thyroidectomy consistently showed damaged follicular cells ranging from slight degenerative changes to total follicular destruction (11, 33–35). Data on MIBI scintigraphy in different forms of destructive thyrotoxicosis are very limited. In apparent contrast with our findings, Hiromatsu *et al.* (36) reported significant MIBI uptake in the early phase of subacute thyroiditis, the more common form of destructive thyrotoxicosis. However, this uptake was apparently related with the severe inflammatory process leading to granuloma formation of subacute thyroiditis and independent from thyroid follicular cell destruction. In keeping with this notion, the marked MIBI uptake is observed in other granulomatous lesions such as sarcoidosis (37). In contrast with subacute thyroiditis, the histological examination of all glands from AIT patients submitted to thyroidectomy did not show relevant inflammatory processes, with the exception of minimal lymphocytic and plasmacellular infiltration (11, 33–35, 38). A further difference between AIT and subacute thyroiditis is represented by the long-term incidence of hypothyroidism that is more frequent in AIT patients (39). The faint or transient MIBI uptake observed in AIT Ind may perhaps be explained by incomplete thyroid destruction associated with different degrees of hyperfunctioning tissue.

The comparison of the diagnostic power of MIBI scintigraphy with the other instrumental procedures employed in this study in differentiating AIT I from AIT II provided interesting results. First of all, MIBI scan was much more accurate than $^{99m}\text{TcO}_4^-$ scintigraphy, which was positive only in one of the six patients with AIT I with a 'hot' thyroid nodule, while no imaging was obtained with all the other subjects. This confirms the low diagnostic value of $^{99m}\text{TcO}_4^-$ scintigraphy in AIT, in keeping with a recent observation of a $^{99m}\text{TcO}_4^-$ 'hot nodule' associated only with a transient form of AIT (40). MIBI scintigraphy was also superior to RAIU in the diagnostic evaluation of AIT. In fact, although in our study RAIU was detectable at low values in every AIT I case, low but detectable RAIU was also present in four out of the ten patients who fulfilled all other criteria for AIT II and in three out of the four patients with AIT Ind. In our study, RAIU uptake in AIT I remained very low in all cases, without reaching the levels (up to 40–60%) observed in previous reports carried out on larger number of patients (14, 17). The reason of such discrepancy is not immediately clear, but it may merely be due to the low number of AIT I patients included in the present series, in keeping with the most recent surveys showing that AIT II is by far more frequent than AIT I, which presently accounts for up to 90% of cases of AIT (41). In any case, this is a further element favouring MIBI scintigraphy that was clearly positive even in AIT I glands that did not display significant iodine uptake. Finally, as reported in several previous studies, we confirmed that CFDS is a very useful tool in the differentiation of AIT I (where thyroid blood flow is normal or increased) from AIT II (where thyroid blood flow is decreased) (6, 13, 14, 16). However, although this procedure was able to correctly identify all cases of AIT I, significant parenchymal (two cases) or nodular (one case) blood flow was detected in three patients with a final diagnosis of AIT II.

In conclusion, this study shows that MIBI scintigraphy can be proposed as an easy and highly effective diagnostic tool for the differential diagnosis of AIT, with positive persistent scans in AIT I and negligible uptake in AIT II. MIBI scintigraphy appears also to give some insights into indeterminate forms of AIT.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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