Amiodarone-Induced Thyrotoxicosis

Differential Diagnosis Using ^{99m}Tc-SestaMIBI and Target-to-Background Ratio (TBR)

Simona Censi, MD, Valentina Bodanza, MD,† Jacopo Manso, MD,* Sara Gusella, MD,† Sara Watutantrige-Fernando, MD,* Elisabetta Cavedon, MD,* Susi Barollo, PhD,* Loris Bertazza, PhD,* Diego Cecchin, MD,† and Caterina Mian, MD, PhD**

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Purpose of the Report: Distinguishing between amiodarone-induced thyrotoxicosis (AIT) caused by excessive hormone synthesis (AIT-1) or by a destructive process (AIT-2) has important therapeutic implications, but is still difficult and debated. ^{99m}Tc-sestaMIBI thyroid scintigraphy (99m-STS) has been proposed as a tool for classifying the two forms.

Material and Methods: 30 AIT patients (11 females and 19 males) who underwent 99m-STS were retrospectively assessed for the present study. For each patient, a target-to-background ratio (TBR) was obtained on planar images. The TBR was then correlated with the qualitative assessment of the scans and the final clinical diagnosis.

Results: Considering clinical response to treatment as the gold standard for differential diagnosis, 14 cases of AIT-1, 12 of AIT-2, and 4 mixed forms were identified. 99m-STS was able to qualitatively identify all the mixed forms, while 1/14 AIT-1 and 6/12 AIT-2 cases were misdiagnosed as mixed forms. When the quantitative index (the TBR) was compared with the final clinical diagnosis, ROC curve analysis enabled us to identify an IBR of 0.482 during 99m-STS as a cut-off capable of discriminating between AIT-1 and AIT-2, with 100% specificity and 91.7% sensitivity ($P < 0.0001$, area under the curve: 0.982).

Conclusions: Taking the TBR into consideration, 99m-STS proved a very useful tool for distinguishing AIT-1 from AIT-2, and thus offering patients appropriate treatment as of their diagnosis. This approach can avoid pointless and potentially dangerous combined overtreatments, and may speed up the return to normal thyroid function, which is crucial in AIT patients suffering from heart disease.

Key Words: amiodarone-induced thyrotoxicosis, ^{99m}Tc-sestaMIBI thyroid scintigraphy, target-to-background ratio, amiodarone

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Amiodarone is an iodine-rich class III anti-arrhythmic drug (containing 75 mg of iodine per 200 mg tablet) that is extensively used to treat ventricular arrhythmias and atrial fibrillation, and to maintain sinus rhythm after cardioversion of atrial fibrillation. Its lipophilicity enables amiodarone and its principal metabolite, desethylamiodarone (DEA), to accumulate in the adipose tissue, lung, and thyroid,[1] and it influences thyroid function. Amiodarone and DEA have a very long elimination half-lives (40 ± 10 days and 57 ± 27 days, respectively) and a large volume and tissue distribution. This data together explain why the drug and its metabolites remain available for a long time period after amiodarone withdrawal.[2] There is an abundance of literature reporting a constant reduction in the serum levels of triiodothyronine (T3), an increase in thyroxine (T4) and reverse triiodothyronine (rT3), and a transient increase in thyroid stimulating hormone (TSH) in the first months of treatment, in nearly all patients treated with amiodarone.[3] These effects are due to the drug's capacity to inhibit pituitary and peripheral T4 to T3 conversion,[3–5] and are considered non-functional. Many authors recommend different reference ranges for thyroid hormones in amiodarone-treated patients.[6,7] In fact, FT4 levels are elevated, but amiodarone is capable of agonistically binding and blocking thyroid hormone intracellular T3-receptor, ultimately causing a tissue hypothyroidism.[3] Amiodarone causes overt thyroid dysfunction in 15–20% of chronically treated patients, however.[8] The iodine content in amiodarone mediates amiodarone-induced hypothyroidism (AIH), and amiodarone-induced thyrotoxicosis type 1 (AIT-1). The former is due to the thyroid's failure to escape the acute Wolff–Chaikoff effect, and is easily diagnosed and managed with levothyroxine (L-T4) replacement therapy. Overt hypothyroidism needs treatment, but it is not necessary to treat subclinical hypothyroidism, particularly in the elderly.[9] There is no need to discontinue amiodarone for AIH management, if the drug is considered essential for heart rhythm control.[9,10] The latter is due to an iodine-induced excess thyroid hormone synthesis, that occurs mainly in abnormal thyroid glands (nodular goiter, latent Graves' disease) and needs to be differentiated from amiodarone-induced thyrotoxicosis type 2 (AIT-2), a destructive, self-limiting, thyroiditis resulting from the direct cytotoxic effect of amiodarone, and apparently occurring in normal thyroid glands. Distinguishing between AIT-1 and AIT-2 is often a challenge, however, especially as there are also mixed forms with features of both, the pathophysiology of which has yet to be fully elucidated.[11]

Different treatments are needed for the two forms of AIT. If AIT-1 patients are given no treatment, they would still be thyrotoxic after 6–9 months, given Amiodarone slow elimination. Conversely, since AIT-2 is a self-limiting condition, most patients would be euthyroid after 3–5 months.[2] However, AIT can exacerbate the underlying cardiac pathologic condition and is thus associated with high morbidity and mortality.[12–14] So, especially in the elderly and in patients with impaired left ventricular function, euthyroidism should be established as quickly as possible.[9] Thionamides, with or without potassium or sodium perchlorate, are used in AIT-1 to block thyroid hormone production and deplete intrathyroidal iodine stores. These drugs are ineffective in AIT-2 patients, who may be given steroids

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From the Department of Medicine (DIMED), *Endocrinology Unit, and †Nuclear Medicine Unit, University of Padua, Padova, Italy.
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Compliance with ethical standards

Ethical approval: the information contained in and preparation of this manuscript complies with the journal's ethical standards. All studies and diagnostic procedures were performed in accordance with the guidelines in the Declaration of Helsinki, and all patients gave their written informed consent to all the proposed diagnostic procedures. This article does not contain any studies with animals performed by any of the authors.

Correspondence to: Caterina Mian, PhD, Department of Medicine (DIMED), Endocrinology Unit, University of Padua, Via Ospedale n.105, 35128 Padova, Italy. E-mail: caterina.mian@unipd.it.
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for their membrane-stabilizing and anti-inflammatory effects. A combination of methimazole (MMI), potassium or sodium perchlorate (NaClO4 or KCLO4), and steroids is administered in mixed AIT forms.[8] The decision to stop or continue the drug should be taken jointly by the cardiologist and the endocrinologist.[9] In AIT-2 patients, given its self-limiting nature, euthyroidism can be reached irrespective of amiodarone withdrawal. On the other hand, amiodarone continuation was associated, with a prolonged period in reaching euthyroidism and to higher risk in recurrences.[15] The decision to stop or continue amiodarone is more difficult in AIT-1/mixed-AIT patients. In view of the pathogenetic mechanism, related to an excessive and uncontrollerd synthesis of thyroid hormones induced by an iodine overload, its withdrawal is preferred if feasible from the cardiological standpoint.[2,9] It should be better to continue the drug in critically patients, in which amiodarone is effective in control life-threatening arrhythmias. Indeed, although amiodarone is the cause of thyrotoxicosis, given its long half-life, its suspension could be useless in the short term. Moreover, given its antagonistic effect on T3 binding on cardiac receptor, amiodarone can be protective on thyroid hormones cardiac stimulatory effects.[2]

As mentioned before, differentiating between the forms of AIT can prove difficult, and this influences our ability to assure patients the most appropriate treatment to control any thyrotoxicosis, a serious problem in the event of underlying heart disease. Various clinical, biochemical and radiological tools have been proposed to distinguish between AIT-1 and AIT-2. Some data in the literature suggest that AIT-1 is associated with: an underlying thyroid abnormality on physical examination or ultrasonography (nodular goiter or latent Graves' disease)[8]; a normal to high thyroid radioactive iodine uptake (RAIU) despite a high urinary iodine excretion[16]; normal to slightly-elevated serum interleukin-6 (IL-6) levels[17]; high levels of anti-thyroglobulin (TgAb), anti-thyroperoxidase (TPOAb) and/or anti-TSH receptor (TRAb) antibodies, suggestive of thyroid disease[18]; and an increased vascularity on color flow Doppler sonography (CFDS).[19] Conversely, a patient with no detectable thyroid abnormalities, markedly high IL-6 levels, and a low or absent RAIU, who tests negative for thyroid antibodies, and shows no vascularity on CFDS is likely to be a case of AIT-2. The final AIT etiology nonetheless often remains dubious, even after combining such differential and complementary laboratory tests and imaging tools as much as possible. In 2008, Piga et al produced promising preliminary results suggesting that ^{99m}Tc-methoxy-isobutyl-isonitrile (sestaMIBI) uptake on scintigraphy (99m-STS) uptake by the thyroid can be used to distinguish AIT-1 from AIT-2.[20] The rationale behind this use of 99m-STS lies in that sestaMIBI is accumulated by mitochondria-rich cells, whereas necrotic and apoptotic tissues are unable to take up the sestaMIBI tracer because their mitochondrial membrane potential has collapsed. In their series of 20 patients, Piga et al found a normal or increased 99m-STS uptake in all of the 6 AIT-1 patients, no uptake in any of the 10 patients with AIT-2, and an intermediate uptake pattern in patients with mixed forms. The authors concluded that 99m-STS is a highly effective tool for the differential diagnosis in this setting, and better than CFDS or RAIU. In another series of 15 patients, Wang et al obtained comparable results.[21] Unfortunately, to our knowledge, these findings have never been confirmed in larger series, and using a prospective study design.

The aim of the present study was to analyze the usefulness of 99m-STS in the differential diagnosis of AIT in a large, monocentric series of consecutive patients who were prospectively followed up. In addition, the qualitative analysis of uptake on planar images was improved by applying a quantitative index in an effort to enhance the diagnostic performance of this approach, and to identify a possible cut-off for distinguishing between AIT-1 and AIT-2.

SUBJECTS AND METHODS

Study Design and Patients

The present retrospective study involved a total of 30 consecutive AIT patients [11 females and 19 males; age ± standard deviation (SD): 67.2 ± 9 years, range 49–80 years] referring to our Endocrinology Unit between June 2010 and May 2017. The diagnosis of AIT was based on: clinical data (signs and symptoms of thyrotoxicosis); laboratory findings, including increased serum levels of free T4 (FT4), high or in the upper-normal range free T3 (FT3), undetectable or low serum concentrations of thyroid stimulating hormone (TSH), and a recent history of amiodarone treatment (ongoing or withdrawn less than 1 year previously). In every cases urinary iodine excretion (UIE) confirmed very high levels of urinary iodine (data not shown). AIT developed from 1.7 to 180 months after starting amiodarone therapy.

FT4, FT3, and TSH were measured in all patients. AbTG, AbTPO and TRAb were available for 28/30 subjects. All patients underwent thyroid ultrasound (Hitachi EUB 7500, Hitachi Medical Corporation 4-14-1, Soto-kanda, Chiyoda, Tokyo, Japan) with a 7.5 mHz linear electronic transducer. CFDS findings were available for 26/30 patients, with color gains individually adjusted to avoid artifacts. Thyroid function was measured approximately every 15 days until patients were stabilized. All patients underwent 99m-STS at the Nuclear Medicine Unit of Padua to differentiate between the AIT subtypes on the basis of a qualitative tracer uptake assessment. A quantitative assessment was also obtained for each patient, based on a target-to-background ratio (TBR) calculated on the early planar images (after 15 min).

Patients with an initial diagnosis suggestive of AIT-1 were treated with MMI, possibly associated with $NaClO_4$ or $KCLO_4$. Patients with an initial diagnosis suggestive of AIT-2 were treated with prednisone (Pd). A final diagnosis was established on the grounds of patients' response to treatment. If they did not reach euthyroidism with the therapy they were given in the light of their initial diagnosis, and a combined treatment (MMI ± $NaClO_4$/$KCLO_4$ and Pd) proved necessary for thyroid hormone control, patients were reclassified as having mixed forms of AIT. One patient initially diagnosed with a mixed form of AIT and treated with the combined therapy without achieving hormone normalization underwent thyroidectomy for thyroid function control.

All studies and diagnostic procedures were performed in accordance with the guidelines in the Declaration of Helsinki, and all patients gave their written informed consent to all the proposed diagnostic procedures.

Assays

Serum TSH, FT3, FT4 (Roche, Rotkreuz, Switzerland); AbTG and AbTPO (DiaSorin, Stillwater, MN); TRAb (EuroImmun, Luebeck, Germany) were tested with commercial kits. Normal values were: TSH: 0.2–4 mIU/L; FT3: 3.90–6.80 pmol/L; FT4: 9.00–22.00 pmol/L; AbTG: 0.0–100.0 kU/L; AbTPO: 0.0–30.0 kU/L; TRAb: <1.1 IU/L.

Thyroid ^{99m}Tc-SestaMIBI Scintigraphy

99m-STS was performed with a dual-head gamma camera equipped with low-energy, high-resolution collimators (Infinia, GE Healthcare), or a triple-head gamma camera equipped with low-energy, ultra-high-resolution collimators (Irix Marconi, Philips) after intravenous injection of about 350 MBq (9.5 mCi) of sestaMIBI. Early and late images were acquired, at 15 and 60 min, respectively. A qualitative assessment was based on the pattern of tracer uptake: a diffuse tracer retention in the early images and a complete washout of the radiopharmaceutical in the late images prompted the patient to

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be classified as a case of AIT-1; if there was no significant tracer uptake in the early images, the patient was diagnosed as having AIT-2. A few patients had uptake patterns not clearly attributable to either AIT-1 or AIT-2 forms, and were classified as mixed/AIT-1 (if they had a normal or slightly lower uptake than in AIT-1 in the early images, and only a partial washout in the late images) or mixed/AIT-2 (if they had a slightly higher uptake than in AIT-2 in the early images, and partial or complete washout in the late ones) (Fig. 1). For each patient a target-to-background ratio (TBR) was calculated on the planar images obtained 15 min after intravenous injection of the radiopharmaceutical agent. A rectangular region of interest (ROI) representative of the background activity was drawn on the supraclavicular area and another ROI was drawn contouring the thyroid (target area). A background normalization was performed, based on the following formula:

$$\mathrm{TBR} = (\text{target average counts} - \text{background average counts}) / \text{background average counts}$$

The ratios were obtained by two operators in double-blind manner, and were found comparable.

Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normal distribution of each variable. The t-test and ANOVA were used to measure differences in mean age, FT4 levels at diagnosis, median time to first normalization of FT4 and FT3 levels, and FT4/FT3 ratios at the time of AIT diagnosis. The Mann–Whitney test and the Kruskal–Wallis test for nonparametric data were used to correlate AIT diagnosis and median duration of amiodarone treatment before the onset of thyrotoxicosis, and median FT3 levels at diagnosis. Categorical variables (sex, AbTG/AbTPO, TRAb, CFDS, presence or absence of thyroid nodulations) were compared with the chi-square test. The diagnostic performance of the TBR was assessed by analyzing the receiver operating characteristic (ROC) curve, from which the best statistical cut-off for the TBR was identified, then the sensitivity and specificity of the cut-off were calculated. The diagnostic utility of the test was assessed from the area under the curve (AUC). A P-value of <0.05 was considered significant in all tests. All statistical analyses were performed using MedCalc for Windows, version 17.6.

RESULTS

Patients

Taking patients' response to treatment as the gold standard led to the identification of 14/30 cases of AIT-1, 12/30 cases of AIT-2, and 4/30 mixed forms. Patients' clinical and biochemical features are given in Table 1. The median time to the onset of thyrotoxicosis after starting amiodarone treatment was 21 months in the AIT-1 group (range: 1.7–180 months), 36 months in the AIT-2 group (range: 11–84 months), and 16.5 months in the group with mixed forms (range: 3–48 months). There was a trend towards a longer amiodarone therapy duration in AIT-1 then AIT-2, but it did not reach statistical significance ($P = 0.07$). The mean time to first normalization of FT3 and FT4 levels did differ significantly, however, between the three groups: FT4 levels normalized in 94.5 days in patients with AIT-1, in 65.4 days in those with AIT-2, and 177.3 days in those with mixed forms ($P = 0.013$); FT3 levels returned to normal after 110.5 days, 46.9 days, and 158.7 days, respectively ($P = 0.011$). The three AIT groups did not differ in terms of median FT3 and FT4 levels at diagnosis, FT4/FT3 ratio, sex, age, presence of TGAb, TPOAb, TRAb, or presence of thyroid nodules (Table 2). 7/30 patients were still taking amiodarone when 99m-STS was performed. Among these patients, 2/7 (patients 5 and 6), never withdrew amiodarone because of cardiologic contraindications. The other patients (patients 2, 7, 15, 22 and 23) discontinued amiodarone few days after 99m-STS was performed. 12/30 patients were taking an empiric treatment for thyrotoxicosis when 99m-STS was performed.

Color Flow Doppler Sonography (CFDS)

CFDS findings were available for 13/14 AIT-1 patients, 9/12 AIT-2 patients and all 4 patients with mixed forms. The patients with AIT-2 all lacked, or had minimal spots of intraparenchymal vascularization, indistinguishable from the pattern seen in a normal thyroid. The same was true of all the patients with mixed forms, and 5/13 with AIT-1. Two of the 13 AIT-1 patients showed perinodular vascularization, 5/13 a slightly increased vascularization, and 1/13 a markedly increased vascularization. CFDS was able to discriminate between AIT-1 and AIT-2 ($P = 0.034$) whenever there was some degree of vascularization (Table 2).

^{99m}Tc-SestaMIBI Scintigraphy in AIT, Qualitative Assessment

As shown in Table 1, all but one of the 14 patients with a final diagnosis of AIT-1 showed a clear, diffuse tracer retention; one of them showed also an area of relatively greater uptake corresponding to a hyperfunctioning nodule nodulation of 30 mm in its largest diameter (patient 27). The remaining AIT-1 patient (patient 29) showed a pattern compatible with mixed/AIT-1 form. No significant uptake was seen in 6/12 patients with a final diagnosis of AIT-2, while the other six revealed a slightly higher uptake than in AIT-2, and were thus scintigraphically classified as cases of mixed/AIT-2. Among

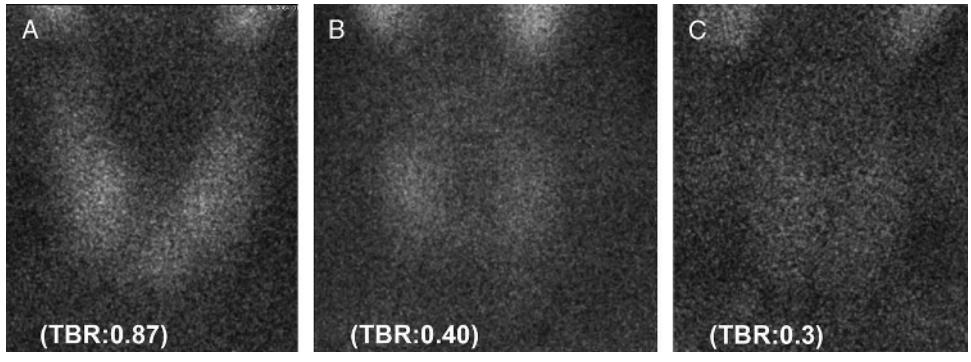

FIGURE 1. Representative images and respective target-to-background ratio (TBR) of (**A**) amiodarone-induced thyrotoxicosis type-1 (AIT-1), (**B**) mixed AIT and (**C**) AIT-2 on early (15 minute) thyroid 99m-STS.

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TABLE 1. Clinical Features, Instrumental Data and TBR of 30 Patients with Amiodarone-Induced Thyrotoxicosis

Pts	Age (years)	Sex	Duration of Amiodarone Therapy (months)	TSH (mUI/L)	FT4 (pmol/L)	FT3 (pmol/L)	FT4/ FT3	AbTPO	AbTG	TRAb	CFDS	Nodes	99m-STS	Therapy	Final Diagnosis	Outcome FT4 (days)	Outcome FT3 (days)	TBR
1	52	M	34	0.01	100	36.1	2.7	<1	<10	4.7 → 10.9 → 0.5	0	0	1	MMI + $KClO_4$	1	79	79	0.502
2	75	M	36	0.01	47.8	8	5.9	<1	<10	1.1 → 1.5 → 0.9	0	0	Mixed/2	MMI[1] + Pd	2	90	89	0.524
3	76	M	24	0.01	57.36	10.69	5.3	2.3	<10	1 → 1.3 → 0.7	0	2	2	MMI[1] + Pd	2	82	13	0.349
4	68	M	2	0.01	33.96	7.31	4.6	<10	<10	1.1 → 0.8	2	2	1	MMI + $KClO_4$	1	162	162	0.868
5	60	F	48	0.03	32.18	4.45	7.2	188	<10	0.9 → 0.3	0	0	Mixed/2	No therapy	2	41	40	0.482
6	80	M	84	0.08	24.54	4.92	4.9	<10	<10	<0,1	nd	0	Mixed/2	Pd	2	8	—	0.39
7	78	F	36	0.02	64.98	10.97	5.9	<10	<10	0.5	0	2	Mixed/2	MMI[1] + Pd	2	7	5	0.41
8	61	M	1.7	0.01	57.93	15.09	3.8	76.3	123.9	3.4 → 3.6	3	0	1	Pd[2] + MMI + $NaCLO_4$	1	181	181	0.55
9	49	M	84	0.04	27.16	8.19	3.3	nd	nd	0.3	0	1	1	Pd[2] + MMI	1	161	161	0.490
10	75	M	24	0.01	66.64	10.99	6.06	2.9	418.8	<0.1 → 1.3	1	0	1	MMI	1	53	53	0.64
11	77	M	36	0.01	68.35	9.8	6.9	14.5	19.5	0.3 → 0.5	0	0	Mixed/2	Pd + MMI[3]	Mixed	Surgery	Surgery	0.383
12	71	F	60	0.01	32.93	5.42	6.08	<10	<10	0.2 → 0.7	nd	2	Mixed/2	Pd	2	71	—	0.454
13	63	M	3	0.04	27.25	8.04	3.39	9.9	<10	1.1 → 0.3 → 1.2	0	0	Mixed/1	MMI + Pd + $NaClO_4$[4]	Mixed	119	63	0.56
14	60	F	29	0.01	43.78	12.26	3.6	21	<10	0.6	0	2	Mixed/2	MMI[1] + Pd	2	44	44	0.322
15	71	M	48	0.01	28.44	6.28	4.53	<1	52.6	0.6	0	0	1	MMI	1	8	—	0.501
16	61	F	11	0.01	69.36	16.1	4.31	2	<10	0.3	0	1	2	Pd	2	57	18	0.355
17	51	M	25	0.01	99.11	23.12	4.2	nd	nd	nd	0	2	2	Pd	2	79	79	0.313
18	68	F	24	0.01	39.38	6.83	5.7	339	69	0.7	1	2	1	MMI + $KClO_4$	1	33	33	0.633
19	67	M	36	0.01	77	13.52	5.7	<10	<10	nd	nd	2	2	Pd	2	90	90	0.367
20	71	F	2	0.01	58.96	9.73	6.05	<10	<10	0.6	nd	2	1	MMI	1	130	130	1.053
21	77	M	9	0.01	74.08	11.12	6.66	<10	14	<0.1	0	0	Mixed/1	MMI + $NaClO_4$ + Pd[4]	Mixed	117	117	0.616
22	55	F	180	0.01	32.09	4.8	6.69	11.6	79.4	0.3 → 0.6	1	2	1	MMI + Pd[2]	1	2	—	0.56
23	69	M	18	0.01	30.64	4.96	6.5	4.3	<10	<0.1	1	1	1	MMI + $NaClO_4$	1	69	—	1.522
24	69	M	48	0.01	85.5	14.97	5.7	28.3	<10	0.3 → 0.9	0	0	Mixed/2	MMI + Pd[3]	Mixed	296	296	0.404
25	57	M	24	0.07	30.65	4.76	6.4	5.4	58.1	0.4	0	0	2	Pd	2	81	—	0.374
26	59	F	25	0.01	43.44	9.15	4.74	341.8	266.4	0.7	0	0	1	MMI + $NaClO_4$	1	136	136	0.784
27	76	F	10	0.01	36.99	7.14	5.2	1.5	<10	0.4	2	2	1	MMI + $NaClO_4$	1	126	126	0.626
28	74	M	18	0.01	45.79	12.09	3.79	1.1	<10	0.5	1	0	1	MMI + $NaClO_4$	1	104	76	1.055
29	71	M	15	0.01	31.48	4.00	7.87	26	<10	0.2	0	0	Mixed/1	MMI	1	79	79	0.7
30	79	M	28	0.01	53.85	9.03	5.96	1.5	<10	0.4	0	0	2	Pd	2	113	44	0.39

Normal values: TSH: 0.2–4 mUI/L, FT3: 3.90–6.80 pmol/L, FT4: 9.00–22.00 pmol/L, AbTPO: 0–30 kU/L, AbTG: 0–100 kU/L, TRAb: <1.1.

CFDS: 0: vascularization not increased, 1: slightly increased vascularization, 2: perinodular vascularization, 3: markedly increased vascularization. Nodes: 0: absent nodes, 1: uninodular goiter, 2: multinodular goiter. Diagnosis: 1: amiodarone-induced thyrotoxicosis type 1, 2: amiodarone-induced thyrotoxicosis type 2. Therapy: 1: initially treated for few days with MMI at diagnosis, then stopped soon after 99m-STS was performed; 2: initially treated for few days with MMI and Pd at diagnosis, before 99m-STS was performed; then Pd was stopped. 3: Initially treated with Pd alone, with unsatisfactory response. 4: Initially treated with MMI and $NaClO_4$ with unsatisfactory response.

Abbreviations: 99m-STS, ^{99m}Tc-methoxy-isobutyl-isonitrile uptake on scintigraphy; AbTG, anti-thyroglobulin; AbTPO, anti-thyroperoxidase; TRAb, anti-TSH receptor; CFDS, color-flow Doppler sonography; FT3, serum free triiodothyronine; FT4, serum free thyroixine; nd, not determined; MMI, methimazole; $NaClO_4$, sodium perchlorate; $KClO_4$, potassium perchlorate; Pd, prednisone; TBR, target-to-background ratio.

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TABLE 2. Clinical, Biochemical and Instrumental Features of the Study Group

Variables	AIT-1 (n = 14)	AIT-2 (n = 12)	Mixed (n = 4)	*P*
Sex (female/male)	6/8	4/8	0/4	0.299
		$P = 0.760$		
Age (years)	65.7 ± 8.9	67.9 ± 9.9	70.7 ± 7.5	0.625
		$P = 0.555$		
Mean (±SD) basal FT4 (pmol/L)	45.2 ± 20.0	52.8 ± 22.1	63.8 ± 25.3	0.303
		$P = 0.368$		
Median basal FT3 (pmol/L)	7.8	9.9	10.5	0.519
		$P = 0.681$		
Mean (±SD) FT4/FT3	5.1 ± 1.5	5.6 ± 1.0	5.7 ± 1.6	0.612
		$P = 0.368$		
TGAb and/or TPOAb	4/13	1/11	0/4	0.232
		$P = 0.252$		
TRAb	4/14	2/10	1/4	0.892
		$P = 0.095$		
CFDS	5/13: not increased 5/13: slightly increased 2/13: perinodular 1/13: markedly increased	9/9: not increased	4/4: not increased	0.072
		$P = 0.034$		
Nodules	7/14	7/12	1/4	0.513
		$P = 0.532$		
Median duration of amiodarone treatment (months)	21	36	16.5	0.138
		$P = 0.07$		
Mean (±SD) time to the first normalization of FT4 (days)	94.5 ± 57.6	65.4 ± 33.9	177.3 ± 102.8	0.013
		$P = 0.138$		
Mean (±SD) time to the first normalization of FT3 (days)	110.5 ± 48.9	46.9 ± 32.5	158.7 ± 121.9	0.011
		$P = 0.037$		

Normal values: FT3: 3.90–6.80 pmol/L; FT4: 9.00–22.00 pmol/L.

Abbreviations: AbTG, anti-thyroglobulin; AbTPO, anti-thyreoperoxidase; AIT, amiodarone-induced thyrotoxicosis; TRAb, anti-TSH receptor; CFDS, color-flow Doppler sonography; FT3, serum free triiodothyronine; FT4, serum free thyroxine; SD, standard deviation.

the four patients with mixed forms, one (patient 24, Table 1) had a pattern of mixed/AIT-2 uptake, plus an area of nodular uptake, although US was negative for nodules. This inconsistency between scintigraphy and US prompted SPECT/CT analysis, on which the area of elective 99m-STS uptake was located in the cervical vertebrae between C7 and T2 (consistent with arthrosis). Two other mixed forms were classified as mixed/AIT-1, and 1/4 as mixed/AIT-2.

^{99m}Tc-sestaMIBI Scintigraphy in AIT, Quantitative Assessment

When the semi-quantitative index (TBR) was compared with the final clinical diagnosis, ROC curve analysis identified a cut-off for the TBR of 0.482 during 99m-STS for discriminating AIT-2 from AIT-1, with 100% specificity and 91.7% sensitivity ($P < 0.0001$, AUC: 0.982). In fact, 11/12 AIT-2 patients had a TBR of ≤0.482, and 14/14 AIT-1 patients had a TBR >0.482 (Fig. 2).

Scintigraphic Qualitative and Semi-Quantitative Comparison in the Differential Diagnosis of AIT

When the qualitative and the semi-quantitative index (TBR) were compared, the latter proved more accurate. The qualitative assessment identified seven mixed forms that were not confirmed by the patients' clinical evolution and response to treatment (six proved to have AIT-2, and one was a case of pure AIT-1). The TBR, on the other hand, was unable to identify the four mixed forms of AIT.

DISCUSSION

Amiodarone-treated patients invariably have underlying heart diseases, and this makes managing their hyperthyroidism particularly challenging, being hyperthyroidism significantly related to worsening arrhythmia and may be associated with a higher mortality risk in this clinical setting.[8] Short-term follow-up studies have found AIT associated with a higher mortality than thyrotoxicosis due to Graves' disease or multinodular goiter, with AIT emerging as a significant predictor of death[13]; patients with AIT also have a considerably higher morbidity, though no clear cause–effect relationship has been demonstrated as yet.[22]

The difficulty of clearly differentiating AIT-1 from AIT-2 has led authors to advocate a combined therapy,[23–25] or a stepwise approach[26] to ensure euthyroidism, but this takes longer than a tailored treatment, and is not devoid of far from negligible harmful effects in elderly patients.[27] Taking longer to reach euthyroidism implies a longer exposure to thyrotoxicosis, and consequently higher risks of arrhythmia, hospitalization, and cardiovascular events.[27] That is why an effective differential diagnosis between the hyperproductive and destructive forms from the start is so important in the management of patients with AIT.

Unfortunately, all the laboratory and imaging findings advocated in the literature to date may be misleading, making it

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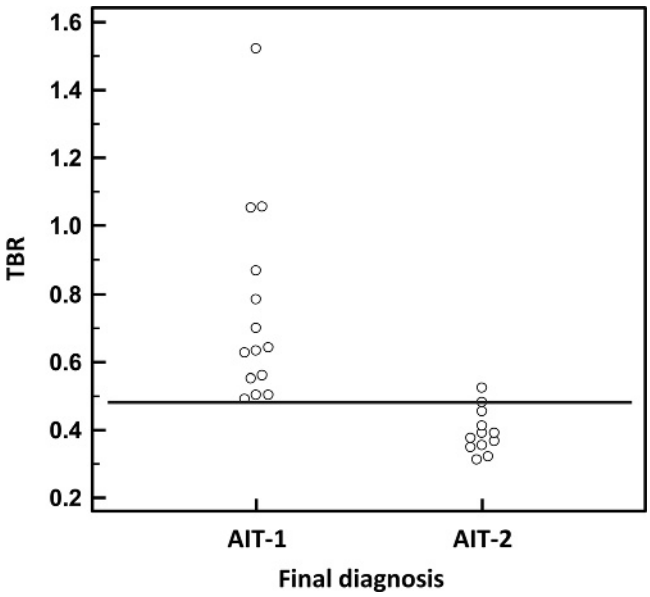

FIGURE 2. Dot plot representation of the TBR obtained in amiodarone-induced thyrotoxicosis type-1 (AIT-1) and in amiodarone-induced thyrotoxicosis type-2 (AIT-2). Sens: sensitivity; Spec: specificity; TBR: target-to-background ratio.

necessary to combine several diagnostic procedures to refine the classification of AIT as much as possible. The presence of goiter or nodules does not necessarily imply an increased thyroid hormone synthesis, gray scale sonographic findings may not be distinctive,[19] and destructive thyroiditis may coexist with a nodular goiter,[13,21] RAIU in AIT-1 and AIT-2 may overlap to some extent, as it is not always completely suppressed in AIT-2, and it is sometimes low in AIT-1.[18,22,23] Many studies have demonstrated that RAIU cannot distinguish efficiently between the two forms of AIT,[20,24,25] possibly due to a different baseline iodide intake in the diet. Bartalena et al advocated using IL-6 to differentiate between AIT-1 subtypes, but it proved useless in several British[26] and American studies,[27] possibly because of reliability issues with commercial assays,[25] or different iodine intakes in the populations studied.

As concerns thyroid autoimmunity, the presence of TRAb is indicative of an underlying Graves' disease, but does not rule out AIT-2.[28] Similarly, AbTG and AbTPO are considered a feature of thyroid disease that points to AIT-1, but a positive titer of these autoantibodies does not rule out AIT-2 either.[25] In many Italian studies (conducted in areas of mild iodine deficiency), CFDS clearly distinguished between forms of AIT,[19] but other studies performed in iodine-replete areas found that CFDS was not always useful.[13]

The aim of our study was to test the utility of 99m-STS in AIT differential diagnosis: our findings confirm previous results,[20] but also reveal some procedural limitations. A qualitative assessment of high 99m-STS uptake was suggestive of a hyperproductive form in all but one of our patients with a final diagnosis of AIT-1, making this diagnostic approach particularly accurate in this category of patients. All the mixed forms were correctly diagnosed by 99m-STS too. On the other hand, only half of the patients finally diagnosed as cases of "pure" AIT-2 were correctly diagnosed as such only with qualitatively evaluation of their 99m-STS uptake. The other half were misdiagnosed as mixed/AIT-2 forms because it proved difficult to distinguish a very faint thyroid uptake from none at all, by comparison with background activity. This means that a considerable proportion of patients with AIT-2 risk being scintigraphically labeled as having mixed forms, and thus receiving useless MMI treatment. This uncertainty had been pointed out in a previous study, which found that a semi-quantitative index—the thyroid-to-background ratio had a better inter-observer reliability than a simple qualitative assessment[28]; the study did not examine the correspondence between final AIT diagnosis and 99m-STS-based qualitative and quantitative diagnoses, however.

The unreliability of 99m-STS prompted us to seek a semi-quantitative parameter, working back from the patients' final AIT diagnosis, that could help to clarify cases revealing no significant 99m-STS uptake. A semi-quantitative uptake index—the TBR, which can quantify thyroid uptake relative to the background—was compared with the final AIT diagnosis by applying a ROC curve analysis, and a cut-off of 0.482 proved sensitive (91.7%) and specific (100%) in distinguishing between AIT-1 and AIT-2. Given the intrinsic nature of a cut-off, the TBR is unable to identify mixed AIT forms, however, so a stepwise approach was needed to maximize the ability of 99m-STS to arrive at a correct diagnosis of AIT (Fig. 3). When a qualitative assessment of the 99m-STS image is clearly compatible with AIT-1 or AIT-2, the diagnosis is extremely accurate, and patients can be treated accordingly. When the qualitative assessment suggests a mixed form, we recommend applying the TBR: a value below the cut-off is indicative of AIT-2, while a higher value suggests a genuine mixed type of thyrotoxicosis. If all 30 of our patients had been classified using this approach, only 4 (13%) would have initially not received a tailored treatment. In our opinion, this is a good result, bearing in mind that it is common practice (for 15% of American and 27% of European thyroidologists, according to a questionnaire-based survey) to treat all patients as if they had mixed forms due to the inability to establish a clear-cut diagnosis.[25]

It should be emphasized that 99m-STS has some advantages over other imaging techniques hitherto applied to the differential diagnosis of AIT. For a start, given the mechanism involved in MIBI uptake, thyroid MIBI scintigraphy is not influenced by thyroid sodium/iodide symporter (NIS) activity or TPO organification processes. 99m-STS can consequently be undertaken even after starting empirical treatment for hyperthyroidism and/or without withdrawing amiodarone (which can sometimes be difficult in critically cardiopathic patients).[8] Indeed, many of the patients in our series were initially given an empiric treatment at AIT diagnosis, before 99m-STS assessment, without any effect on technique

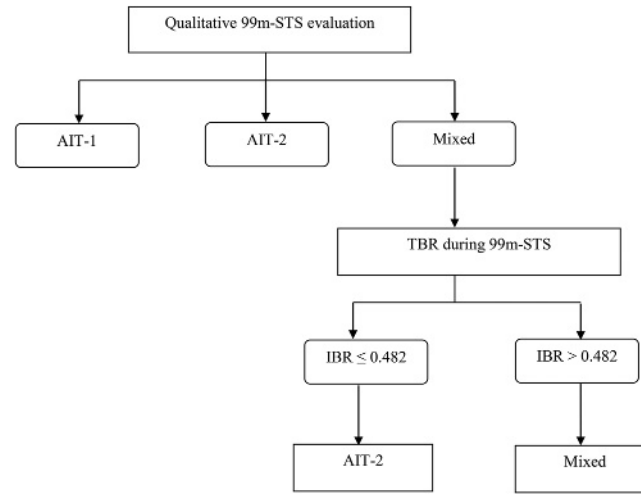

FIGURE 3. Suggested stepwise diagnostic approach based on ^{99m}Tc-sestaMIBI thyroid scintigraphy (99m-STS) in amiodarone-induced thyrotoxicosis (AIT) management; TBR: target-to-background ratio.

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accuracy. Similarly, amiodarone was still ongoing in 7/30 patients when 99m-STS was performed.

Differences in populations' iodine supply have often been mentioned as one of the main reasons for the poor reproducibility of previously considered results, especially for CFDS and RAIU.[8,19,24,26,29] On the other hand, the patients involved in our study came from north-east Italy, a mildly iodine-deficient area, while the study by Piga et al, involved subjects living in an iodine-sufficient area (Sardinia), and the patients examined by Wang et al lived in China, where iodine uptake is adequate.[20,21,30,31] So, whatever the geographical differences in iodine availability, 99m-STS proved equally effective in the differential diagnosis of the various forms of AIT. Second, 99m-STS only takes an hour to complete, and the TBR can easily be calculated in minutes using standard software provided with every gamma-camera. In contrast, it takes at least 24–48 hours to obtain the results of a study on a patient's radioiodine thyroid uptake curve (more accurate the longer the measurement time after ^{131}I administration).[32] CFDS also takes less than an hour to perform, and finding a slightly or markedly increased parenchymal vascularization, or a perinodular blood flow proved highly specific in identifying AIT-1 in our sample. But when vascularization is not increased (and this was the most common pattern in our series), CFDS does not consistently predict glucocorticoid responsiveness, confirming the results reported by another group (24). Finally, the pure gamma emitter tracer Tc99m (used in 99m-STS), with a half-life of 6 h, is much safer than the gamma and beta emitter ^{131}I used in RAIU scintigraphy (which is also burdened with an 8-day half-life).

99m-STS has its limits too. The scarce specificity of the tracer prompted a case of false-positivity in one of our patients, whose arthrosis of the cervical vertebrae mimicked an area of elective nodular uptake in the thyroid parenchyma on planar images. Thyroid US, with CFDS, thus remains a cornerstone in the initial assessment of patients with AIT, and can provide very specific information if there is evidence of increased vascularization.

No specific predictors of the occurrence of amiodarone-associated thyroid dysfunction have been recognized,[33] although female gender and anti-thyroid peroxidase antibodies seem to predict AIH.[34] In view of the risks related to thyroid overt dysfunctions, guidelines generally recommend baseline thyroid function[35,36] and others also thyroid autoantibodies,[36] before amiodarone therapy onset. Patients' thyroid function should be periodically checked, but there is no consensus on the timing of thyroid function tests. Many guidelines recommend to test thyroid function every 6 months, while others are more prudent, suggesting it every 3 months. On the basis of our findings, it should be appropriate to perform thyroid function at the baseline, after 2 months from the beginning and every 6 months thereafter. However, the usefulness of periodic measurements is limited by the often sudden explosive onset of AIT and a normal TSH does not warrant that an AIT can develop in the interval between the two test functions.[2,9]

In conclusion, 99m-STS, combined with the TBR, proved a very useful approach to the classification of AIT, enabling patients to be offered appropriate treatment as soon as they are diagnosed. It can avoid the risk of pointless and potentially dangerous combined overtreatments, and may facilitate a faster return to normal thyroid function, which is crucial in cardiopathic patients.

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