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CHICAGO
MEDICINE &
BIOLOGICAL
SCIENCES

“A 64 year old man with abnormal
thyroid function testing”

Dr. Dickens does not have any relevant
financial relationships with any
commercial interests.

ENDORAMA: Case 1

**A 64 year old man with abnormal
thyroid function testing**

Laura Dickens

April 27, 2017

Objectives

1. Review the spectrum of amiodarone-induced thyroid dysfunction including type 1 and 2 amiodarone-induced thyrotoxicosis (AIT)
2. Evaluate the evidence for using Sestamibi to differentiate type 1 and type 2 AIT
3. Understand the role of adjunctive therapies for refractory AIT

HPI

- 64 year old man with a PMH of CAD s/p CABG (15 years ago), CHF with EF 10%, recurrent VT, HTN, and HLD
- Transfer from Riverside Hospital for recurrent VT and advanced CHF options.
- Developed VT storm, transferred to CCU, on Lidocaine gtt, underwent VT ablation
- TFTs checked and abnormal, Endocrine consulted

What one question do you have?

- Amiodarone?
 - YES
- Additional history
 - Started Amiodarone in 2014
 - TFTs monitored locally by cardiologist, most recently 2 months ago and normal
 - During admission continued on PO amiodarone 200mg BID

PMH:

CAD s/p CABG (15 years ago)

CHF with EF 10%

Recurrent VT

HTN

HLD

PSH:

CABG

VT ablation

Pacemaker

ROS: +palpitations +fatigue
+dyspnea on exertion

Meds:

- Amiodarone 200mg BID
- Aspirin 325mg daily
- Atorvastatin 40mg daily
- Lasix 20mg daily
- Imdur 20mg TID
- Lisinopril 2.5mg BID
- Metoprolol 50mg BID
- Spironolactone 25mg daily
- Famotidine 20mg daily
- Mg and K supplements

Allergies: Ranolazine

Social: Former smoker, 3ppd x40 years, quit in 2014. Occasional wine, no drugs.

Family: Heart disease in father, lung cancer in mother

Physical exam

VITALS: Temp 36.6, BP 99/74, HR 75, RR 22, O2 sat 94 on RA, BMI 28.1

General: No apparent distress. Appears stated age. Sitting in chair.

HEENT: NCAT. No pharyngeal erythema. PERRL. EOMI.

Neck: No neck tenderness. **Thyroid feels mildly enlarged bilaterally, no discrete nodules.**

CV: Normal rate, regular rhythm. Cool extremities. No edema.

Pulm: Clear bilaterally. No increased work of breathing, wheezes, rales.

GI: Soft, non-tender, non-distended abdomen. No rebound or guarding.

MSK: No deformities, no joint swelling. Normal tone.

Neuro: AOx3, no focal deficits.

Skin: No rashes/ulcers.

Psych: Normal mood, thought content. Appropriate.

Admission Labs

138

102

22

97

4.3

25

1.0

Cr baseline 1.0

Ca 9.0

Mg 1.9

Ph 3.5

Thyroid Function Tests

10/23:

TSH 0.36

10/28:

TSH 0.23

Free T4 2.57

T3 113

Total T4 15.8

15.6

8.2

162

Initial Recommendations

- Interpretation of TFTs
 - Consistent with hyperthyroidism
 - Likely recent phenomenon given mild degree of TSH suppression
- Additional tests
 - Check TSI
 - Thyroid ultrasound with dopplers
 - Repeat TFTs in three days
- Treatment: Methimazole 20mg daily

Amiodarone-Induced Thyroid Dysfunction

- Occurs in 15-20% of patients treated with amiodarone
- Spectrum of presentations
 - Hypothyroidism
 - Hyperthyroidism (AIT)
 - Type 1 = iodine-induced hyperthyroidism
 - Type 2 = drug-induced destructive thyroiditis
 - Mixed
- Diagnosis:
 - Labs: T3, free T4, TSH receptor autoantibody
 - Thyroid ultrasound with color flow Doppler
 - Radioactive iodine uptake

AIT: Type 1 vs type 2

TABLE 1. Clinical and pathogenic features of type 1 and type 2 AIT

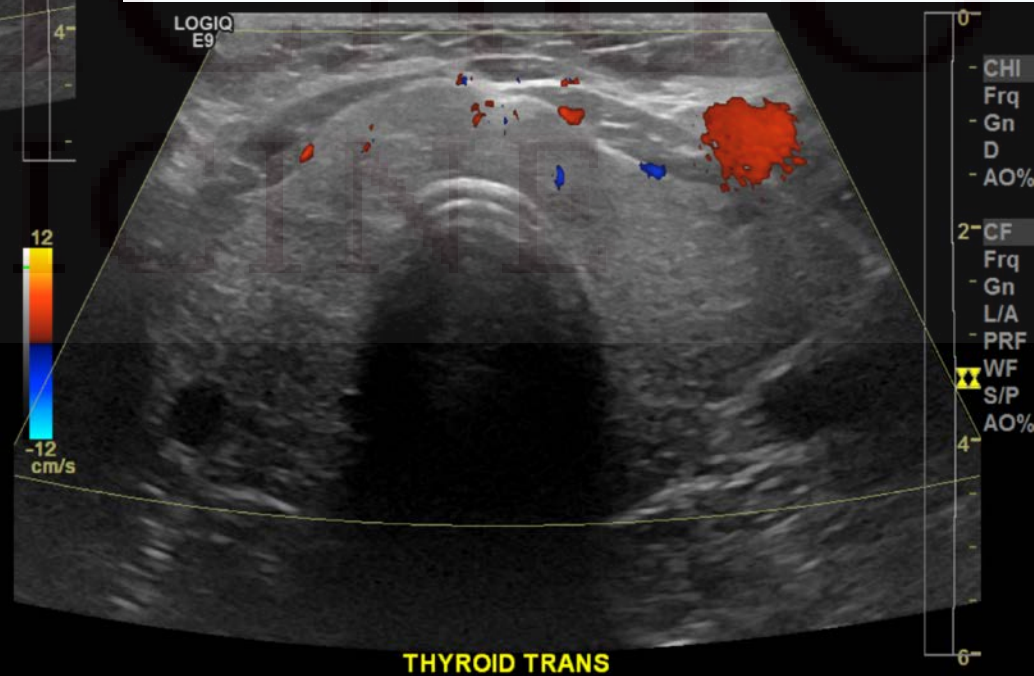
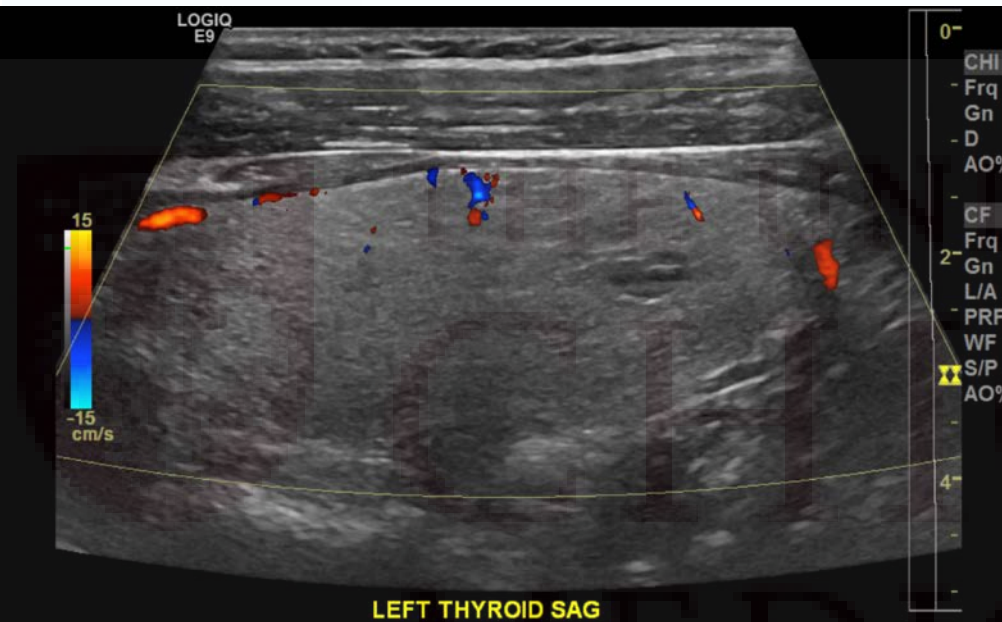
	Type 1	Type 2	Ref.
Underlying thyroid disease	Yes	No	
Thyroid ultrasound	Diffuse or nodular goiter	Normal (hypoechoic) gland (small goiter)	38
CFDS	Increased vascularity	Absent hypervascularity	13
Thyroidal RAIU	Low/normal/increased	Low/absent	39, 40
MIBI	Thyroid retention	Absent uptake	17
Thyroid antibody	Sometimes present	Usually absent	41–43
Pathogenesis	Iodine-induced hyperthyroidism	Destructive thyroiditis	44, 45
Spontaneous remission	No	Possible	47
Preferred medical therapy	Thionamides (plus KClO ₄)	Glucocorticoids	6, 31
Subsequent hypothyroidism	Unlikely	Possible	46
Subsequent therapy for the underlying thyroid disease	Likely	No	

Thyroid Ultrasound 10/31

- Right lobe: 6.4 x 2.5 x 2.7cm. Coarse echotexture.
- Left lobe: 6.6 x 3.4 x 1.9 cm. Coarse echotexture, 6 x 5 mm benign-appearing cystic nodule
- Isthmus: 9mm. 6 x 5 mm benign-appearing thyroid nodule in the right isthmus
- No significant abnormality of parathyroid glands or lymph nodes.
- ADDENDUM: Vascularity of the bilateral thyroid lobes is **unremarkable (low-normal)**

TSI = negative

Thyroid Ultrasound 10/31



	11/1	11/5	11/8	11/12	11/15
TSH	0.22		0.05	0.02	0.01
Free T4	2.54	2.60	2.47	2.78	3.95
T3	121	132	148	155	146
Total T4					
	MMI 20	MMI 30	MMI 40	MMI 30	MMI 40
				Pred 40	Pred 60

Type 1 vs Type 2: Still unclear...

What about a **Sestamibi scan** to differentiate between type 1 and type 2 amiodarone-induced hyperthyroidism?



- A preliminary report utilized ^{99m}Tc -sestaMIBI thyroid uptake and scintigraphy to distinguish type I (normal or increased) from type II (decreased) [39]. If confirmed, this may prove more useful than CFDS.

Sestamibi?

- ^{99m}Tc -sestaMIBI (MIBI) shows increased uptake in epithelial cells with high numbers of mitochondria
- Italian study enrolled 20 patients with AIT and performed thyroid ^{99m}Tc -sestaMIBI (MIBI) scintigraphies along with labs, CFDS, RAIU
- Thyroid ^{99m}Tc -sestaMIBI (MIBI) was superior at differentiating AIT 1 and 2

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CLINICAL STUDY

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

M Piga, M C Cocco¹, A Serra, F Boi¹, M Loy and S Mariotti¹

Nuclear Medicine, Department of Medical Sciences 'M. Aresu', University of Cagliari, c/o Azienda Ospedaliero-Universitaria di Cagliari, Cagliari, SS 554-09042 Monserrato CA, Italy and ¹Endocrinology, Department of Medical Sciences, University of Cagliari, Cagliari, Italy

cosis (AIT).

	CFDS	RAIU (%)	^{99m} Tc Scint	MIBI Scint	Initial AIT diagnosis	Final AIT diagnosis	Therapy	
							MMI KClO ₄	Pd
P1/N2	1	—	+	+	AIT I	AIT I	+	=
P1/N1	1	—	+	+	AIT I	AIT I	+	=
P1/N1	3	—	+	+	AIT I	AIT I	+	=
P1/N1	1	—	+	+	AIT I	AIT I	+	=
P1/N1	2	—	+	+	AIT I	AIT I	+	=
P0/N1	8	+	+	+	AIT I	AIT I	+	=
P1/N1	2	—	Low	+	AIT I	AIT Ind	+	+
P0/N0	3	—	+(w)	+	AIT I	AIT Ind	+	+
P0/N0	0	—	+(w)	+	AIT II	AIT Ind	+	+
P0/N0	1	—	Low	+	AIT II	AIT Ind	+	+
P0/N0	1	—	—	—	AIT II	AIT II	=	+
P0/N0	1	—	—	—	AIT II	AIT II	=	+
P0/N0	0	—	—	—	AIT II	AIT II	=	+
P0/N0	0	—	—	—	AIT II	AIT II	=	+
P0/N0	0	—	—	—	AIT II	AIT II	=	+
P0/N0	0	—	—	—	AIT II	AIT II	=	+
P0/N0	1	—	—	—	AIT II	AIT II	=	+
P1/N0	0	—	—	—	AIT II	AIT II	=	+
P0/N1	0	—	—	—	AIT II	AIT II	=	+
P1/N0	1	—	—	—	AIT II	AIT II	=	+
P0/N0	0	—	—	—	AIT II	AIT II	=	+

Therapy		Outcome Tot (comb) days
MMI KClO ₄	Pd	
+	=	90
+	=	120
+	=	60
+	=	90
+	=	90
+	=	30
+	+	75 (30) ^a
+	+	52 (7) ^a
+	+	50 (30) ^a
+	+	60 (30) ^a
=	+	7
=	+	10
=	+	60
=	+	50
=	+	7
=	+	7
=	+	90
=	+	14
=	+	60
=	+	60

^{99m}TcO₄ scintigraphy; MIBI scint,

ule CFDS pattern; RAIU, radioiodine uptake; ^{99m}Tc scint, thyroid ^{99m}TcO₄ scintigra
: Pd, prednisone, for other details see text.

Table 1 Clinical features, instrumental

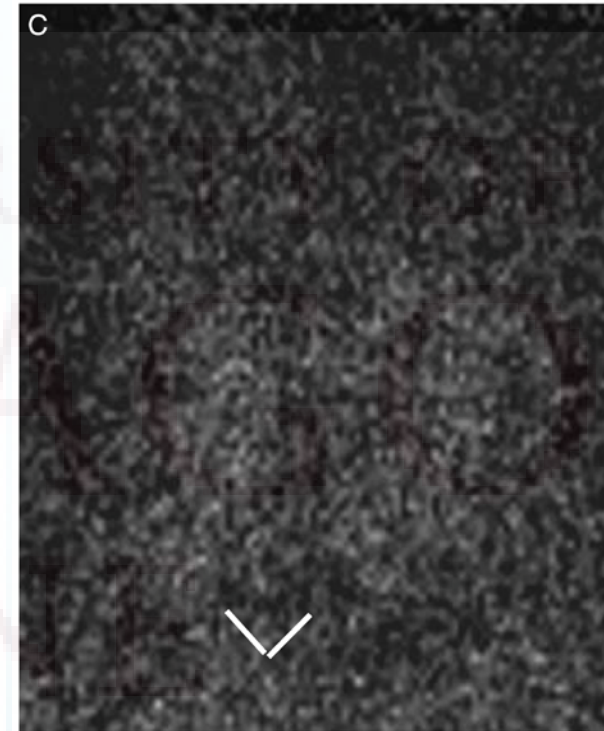
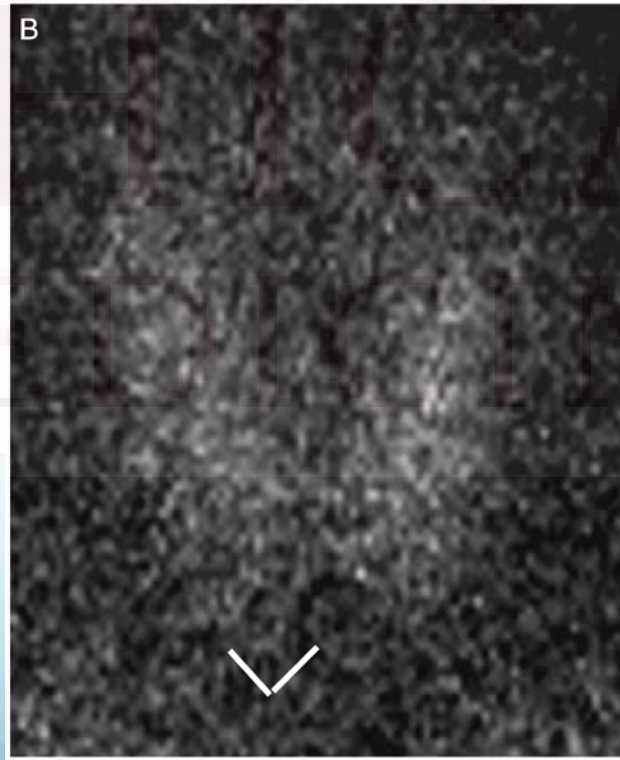
Patients numbers	Age (years)	Sex	AM (g)	TSH (μU/m
1	84	F	140	0.00
2	34	F	144	0.00
3	81	F	16	0.00
4	17	F	142	0.00
5	66	F	140	0.00
6	48	F	280	0.00
7	54	M	140	0.00
8	49	M	34	0.00
9	67	M	142	0.00
10	54	M	70	0.00
11	52	M	140	0.00
12	71	M	210	0.01
13	56	M	210	<0.00
14	64	M	140	<0.00
15	71	M	210	0.00
16	59	M	210	0.00
17	75	M	140	0.00
18	50	M	39	0.00
19	75	M	560	0.00
20	76	M	140	0.00

AM, cumulative amiodarone dose; V, thyroid

^{99m}Tc-sesta MIBI scintigraphy (w, rapid MIBI

^aNumber in parenthesis indicates the number

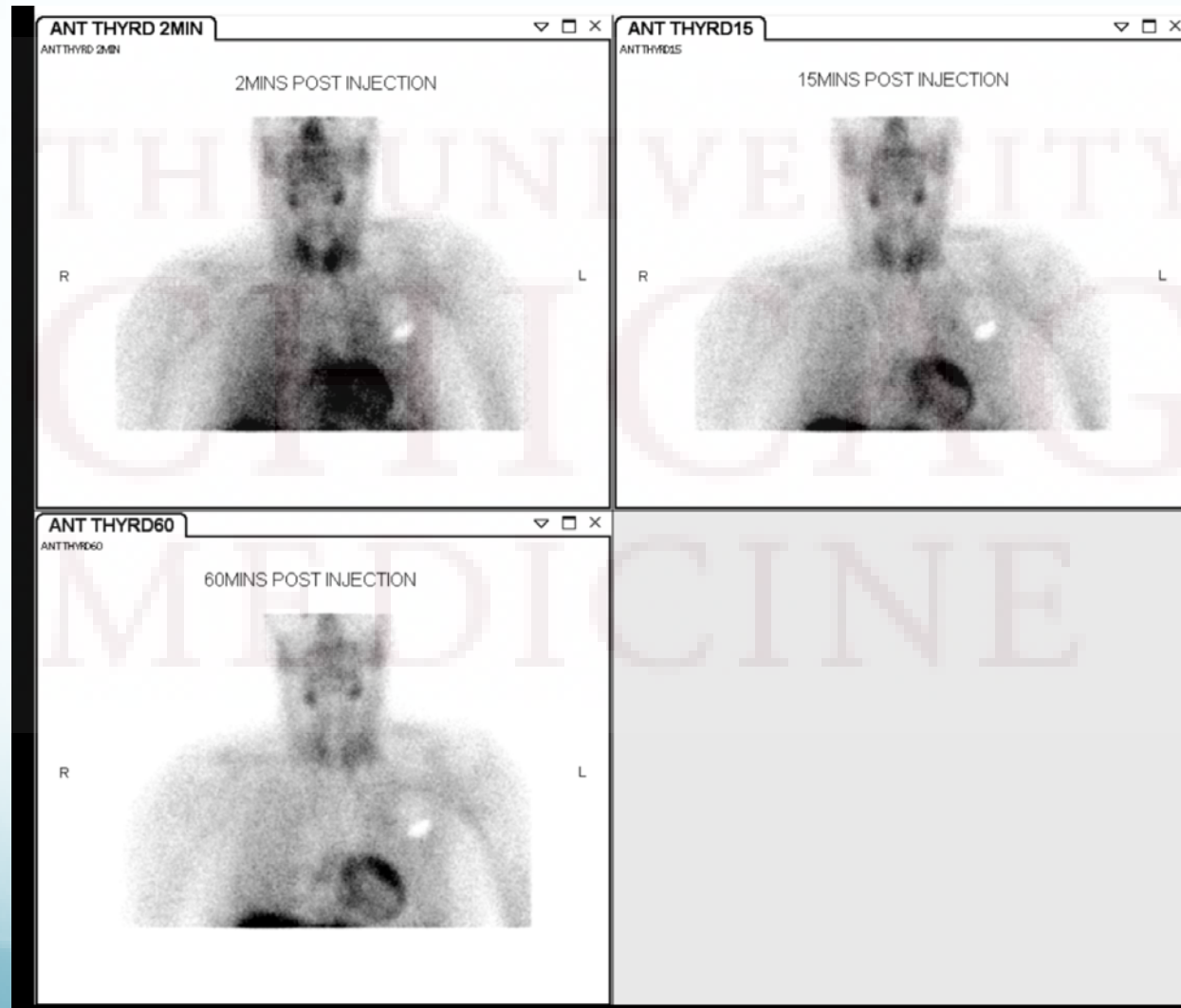
Sestamibi Images from Study



NM Parathyroid Imaging with SPECT

- Technique: 10mCi Tc-99m sestamibi injected IV
- Findings: Normal physiologic uptake in the thyroid at 2 minutes and retained activity at 15 minutes. Washout is seen at one hour.
- Impression: Findings are non-specific but may be consistent with amiodarone-induced thyrotoxicosis **type 1** in the proper setting

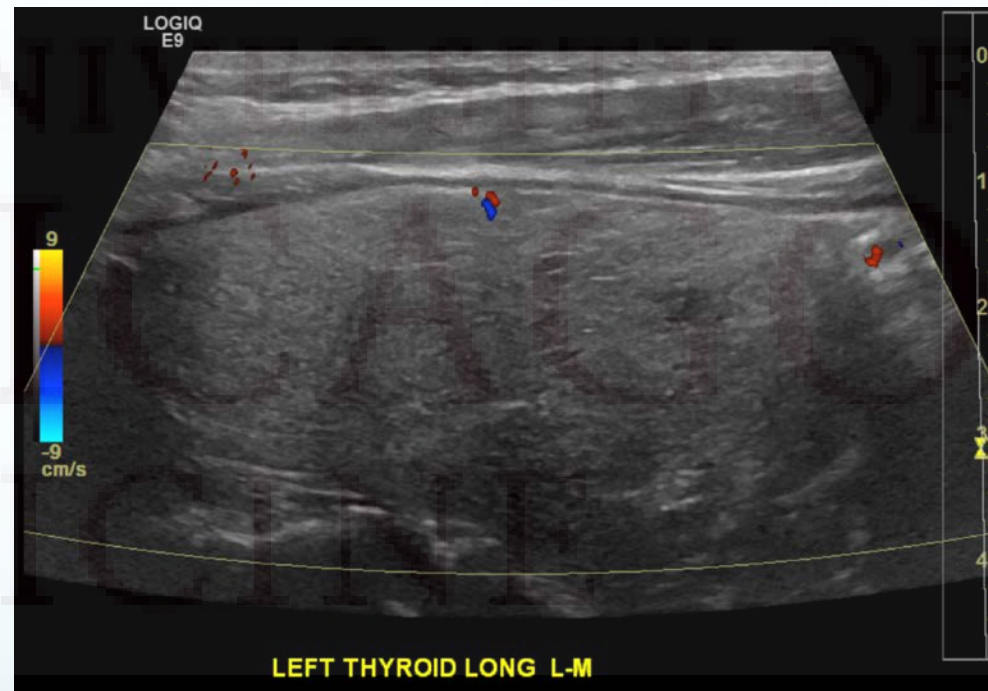
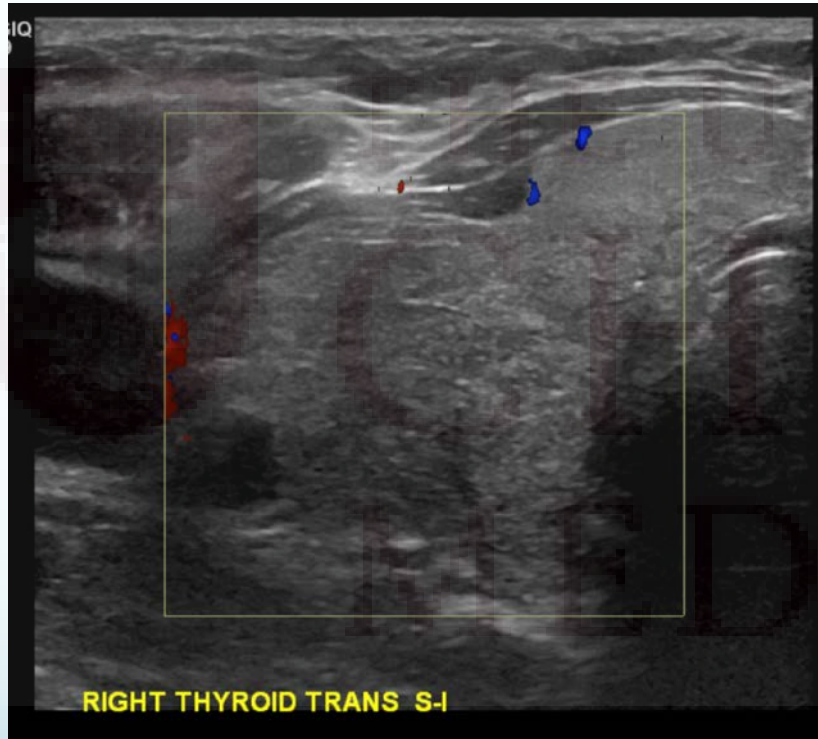
Our Patient's Sestamibi Images

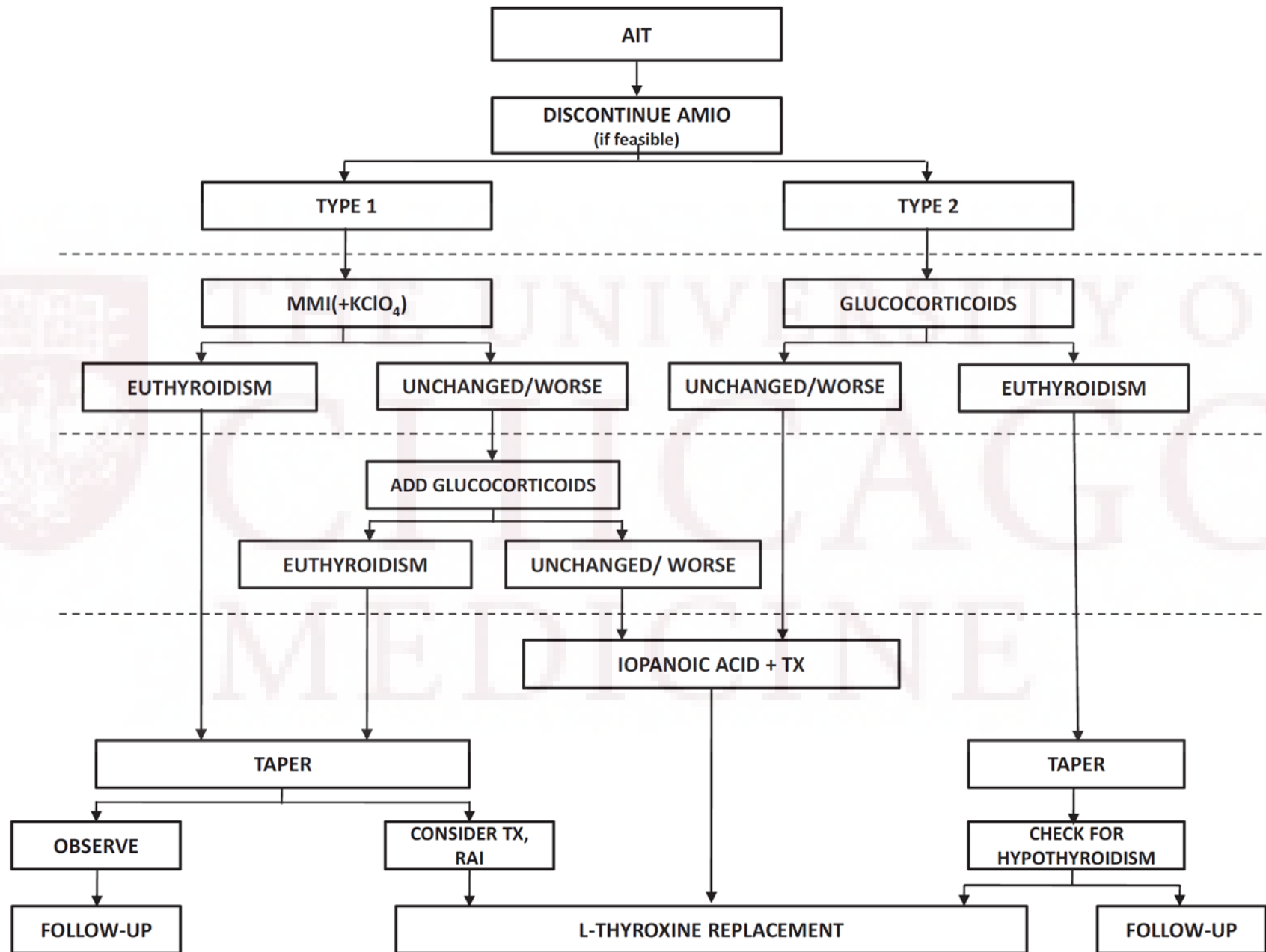


Repeat Thyroid Ultrasound 11/18

- Right lobe: 6.9 x 2.8 x 2.4cm.
- Left lobe: 6.1 x 2.8 x 2.4 cm.
- Isthmus: 8mm.
- Heterogeneous echotexture. Nodules unchanged
- ADDENDUM: Entire thyroid is **poorly vascular**

Thyroid Ultrasound 11/18





Conclusion: Type 2

- Discharged on Prednisone 60mg
- TFTs monitored as an outpatient

	11/18	11/25
TSH	0.01	0.018
Free T4	4.06	2.88
T3	116	100
Total T4	18.5	
	Pred 60	Pred 60

Readmission #1

- Prednisone 60mg resumed
- No further VT on device interrogation
- Amiodarone discontinued

	11/18	11/25	12/16	12/18	12/20
TSH	0.01	0.018	0.01	<0.01	<0.01
Free T4	4.06	2.88	>7.77	>7.77	>7.77
T3	116	100	325	249	201
Total T4	18.5				
	Pred 60	Pred 60	Off Pred	Pred 60	Pred 60

AIT: Other issues

- Amiodarone withdrawal
 - Type 1: 79% of surveyed North American thyroidologists would withdraw
 - Type 2: 66% would withdraw
 - Generally withdrawal favored if “feasible from a cardiological point of view”
- Definitive treatment once euthyroidism achieved
 - Type 1: RAI ablation
 - Type 2: wait and see
- Amiodarone needs to be resumed
 - Type 1: RAI ablation or thyroidectomy
 - Type 2: wait and see

Endo clinic follow up

- Patient is feeling “terrible”
- Complains of weakness, SOB, fluttering in his chest. Using a walker for ambulation.

	12/20	1/3
TSH	<0.01	<0.01
Free T4	>7.77	>7.77
T3	201	142
Total T4		
	Pred 60	Pred 60

What next?

Treating for type 1 and 2

	1/3	1/16	1/28
TSH	<0.01	<0.01	<0.01
Free T4	>7.77	>7.77	>7.77
T3	142	181	191
Total T4		26.0	>24.8
	Pred 60	Pred 60	Pred 60
		MMI 60	MMI 60

Now what?

Thyroidectomy for AIT

Total Thyroidectomy in Patients with Amiodarone-Induced Thyrotoxicosis and Severe Left Ventricular Systolic Dysfunction

Luca Tomisti, Gabriele Materazzi, Luigi Bartalena, Giuseppe Rossi, Angelica Marchello, Manuela Moretti, Luigi De Napoli, Rita Mariotti, Paolo Miccoli, Enio Martino, and Fausto Bogazzi

- 24 patients with AIT who underwent thyroidectomy
 - 9 with type 1, 15 with type 2
- Divided into groups based on LV function
 - LV EF <40, 40-50, >50

TABLE 3. Indications to thyroidectomy

	Group 1 (n = 9)	Group 2 (n = 5)	Group 3 (n = 10)
Worsening of cardiac conditions	8	1	
Thyroid cancer	1		
Unresponsiveness to medical therapy		3	8
Side effects to glucocorticoids			1
Continuation of amiodarone therapy		1	1

Outcomes after Thyroidectomy

TABLE 4. Outcome of mean serum thyroid hormone before surgery

	Group 1 (n = 7)	Group 2 (n = 1)	Group 3 (n = 8)
Basal FT4 (pg/ml)	42.3 ± 19.9	45.1	50.1 ± 15.8
Basal FT3 (pg/ml)	8.9 ± 5.7	7.95	12.1 ± 5.9
Pre-IOPAC FT4 (pg/ml)	69.9 ± 74.1	56.9	45.9 ± 22.3
Pre-IOPAC FT3 (pg/ml)	10.5 ± 7.8	9.57	11.1 ± 6.8
Presurgery FT4 (pg/ml)	53.2 ± 21.1	61.7	48.1 ± 21
Presurgery FT3 (pg/ml)	8.6 ± 6.4	7.74	5.8 ± 3.2

Data are expressed as mean ± sd. Serum FT4 and FT3 concentrations were measured at the diagnosis of AIT (basal value), at the time when the decision of thyroidectomy was made (before IOPAC), and just before surgery. During the period before IOPAC and before surgery, IOPAC was added to the standard medical therapy of AIT in 16 of 24 patients.

TABLE 5. Changes in EF values after restoration of euthyroidism

	Group 1	Group 2	Group 3
EF before surgery (%)	28.2 ± 7.2	42.8 ± 2.4	57.1 ± 3.0
EF after surgery (%)	38.3 ± 6.0	45.0 ± 5.8	59.8 ± 6.6
ΔEF (%)	10.1 ± 7.1 ^{a,b}	2.2 ± 6.1 ^{a,b}	2.7 ± 5.5 ^{a,c}
Improvement, n (%)	4/9 (44.4)	1/5 (20.0)	0/10 (0)
(95% CI, Klopper-Pearson)	(0.137–0.788)	(0.005–0.716)	
<i>P</i>	<0.05		

CI, Confidence interval; ΔEF, mean difference between EF after surgery and EF before surgery.

^a *P* value for intragroup comparison (paired *t* test): *P* = 0.003 for group 1; *P* = 0.470 for group 2; *P* = 0.148 for group 3.

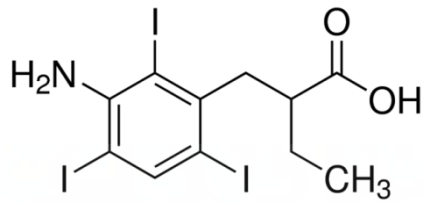
^b *P* value for multiple comparison by Dunnett test: *P* = 0.035 for group1 vs. group 3 (controls); *P* = 0.981 for group 2 vs. group 3.

^c ANOVA *P* = 0.032. Improvement refers to change of EF class.

- Cardiology, Endocrine Surgery, Endocrine discussed options, agreed thyroidectomy was the best option
- Can he safely undergo surgery?
- Can we optimize prior to surgery?

Any ideas?

Iopanoic Acid



- Oral cholecystographic agent
- Inhibits deiodination of T4 to T3
- Results in rapid decrease in T3 levels, little change in T4 levels

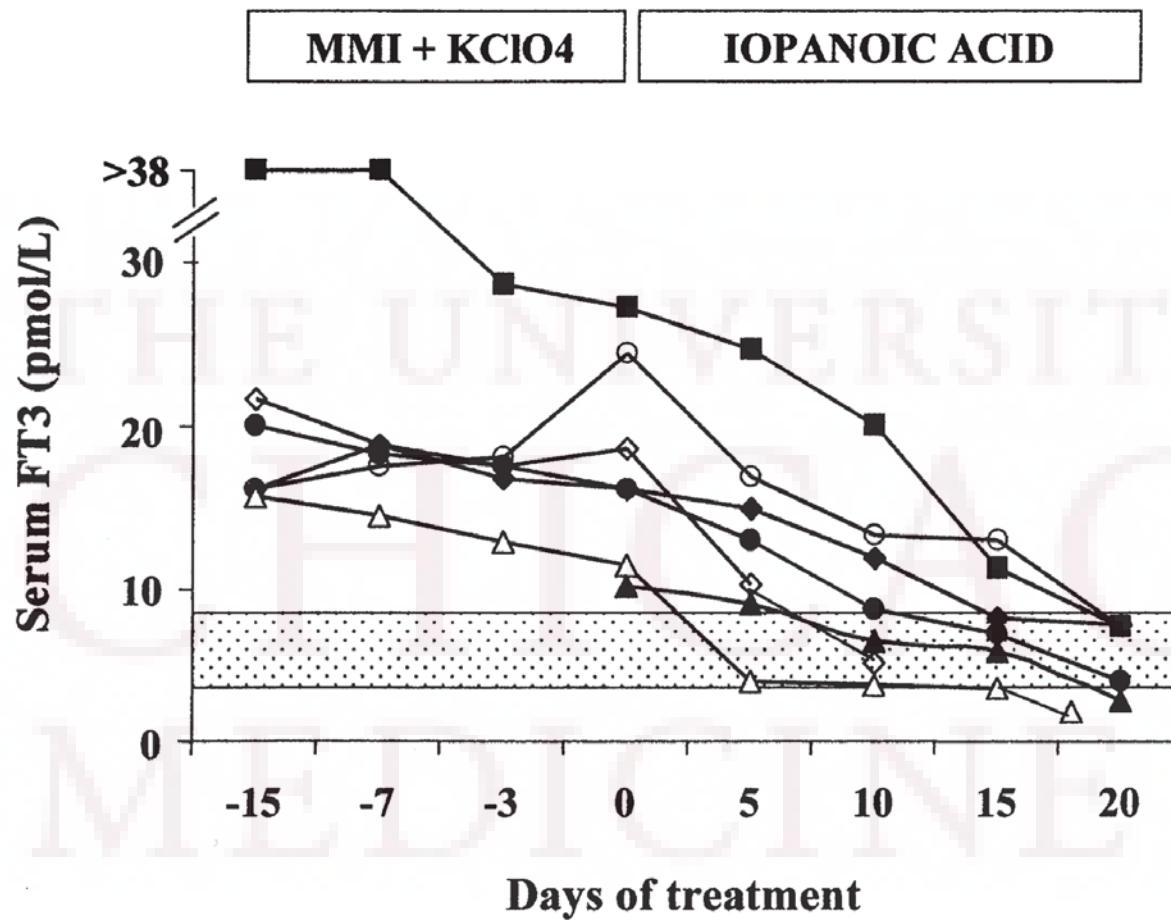


Iopanoic Acid in preparation for thyroidectomy with AIT

Table. Clinical and biochemical features of the patients at baseline

<i>Patient</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>
Sex	M	F	M	M	F	F	M
Age (y)	63	70	71	74	82	73	60
Serum-FT4 (pmol/L)	34	>70	25	>70	43	>70	70
Serum-FT3 (pmol/L)	17	>38	12	23	17	20	12
Serum thyrotropin (mU/L)	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Serum thyrotropin receptor antibody (U/L)	<1	13	<1	<1	<1	<1	<1
Serum thyroglobulin antibody (U/mL)	<5	2689	50	<5	<5	<5	<5
Serum thyroperoxidase antibody (U/mL)	<10	>1000	56	<10	15	<10	<10
Urinary iodine excretion (μg/L)	1625	2778	2178	2012	5500	1976	3120
Thyroid volume (mL)	70	64	91	140	52	37	8
Color flow Doppler sonography (pattern)	I	II	I	I	I	I	0
24-h RAIU, %	23	24	21	19	5	11	0.3
Cumulative dose of amiodarone (g)	Nd	46	18	12	24	72	200
Duration of amiodarone treatment (mo)	4	7	6	3	6	13	36
Type AIT	I	I	I	I	I	I	II

The normal ranges for laboratory values are as follows: FT4, 8.4 to 23.2 pmol/L; FT3, 3.8 to 8 pmol/L; and thyrotropin, 0.4 to 3.7 mU/L. Normal values for serum thyrotropin-receptor antibody are < 1 U/L. Thyroid volume was measured by ultrasonography. Color flow Doppler patterns are as follows: pattern 0, absent hypervascularity; pattern I to III, present to mild and marked increase of thyroidal vascularity. *Nd*, Not determined.



- Sounds like a good option, BUT iopanoic acid is not available in the US

Other ideas for pre-op treatment?

- Lithium
- Cholestyramine
- Plasmapheresis

Admitted for thyroidectomy

	1/28	1/31	2/1	2/2	2/3
TSH	<0.01		<0.01		<0.01
Free T4	>7.77	>7.77	>7.77		7.30
T3	191	164	178		118
Total T4	>24.8	23.5	23.1		21.4
	Pred 60	Pred 60		Stress dose steroids	
	MMI 60	MMI 90		Stop MMI	
	Lithium 150 BID	Lithium 300/150		Stop Lithium	
		Cholestyramine 4g BID		Cholestyramine 4g BID	

Thyroidectomy

Thyroidectomy Pathology: Multiple macrofollicular adenomatoid nodules, largest measuring 0.9cm and 0.8cm

Lab trend, continued...

	2/5	2/6	2/7	2/8	2/14
TSH		<0.01			
Free T4	4.13	2.89	2.26	1.73	1.25
T3	76	64	60	49	
Total T4					
	Pred 40		HC 40/20	HC 20/10	
				L-T4 150	

Case Conclusion

- Clinic 3/17/17
- Patient is feeling “about the same”
- TFTs euthyroid on L-T4 150mcg daily
- Listed for heart transplant

A photograph of a doctor in a white lab coat, with a stethoscope around their neck, holding a red heart-shaped medical model in their hands. The background is a light blue gradient with faint, large text that reads 'THE UNIVERSITY OF CHICAGO MEDICINE'.

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4. Bogazzi F, Miccoli P, Berti P, Cosci C, Brogioni S, Aghini-Lombardi F, Materazzi G, Bartalena L, Pinchera A, Braverman LE, Martino E. Preparation with iopanoic acid rapidly controls thyrotoxicosis in patients with amiodarone-induced thyrotoxicosis before thyroidectomy. *Surgery*. 2002 Dec;132(6):1114-7; discussion 1118. PubMed PMID: 12490863.