A 54-YEAR OLD MALE WITH GRAVES' AND CARDIOMYOPATHY

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HISTORY OF THE PRESENT ILLNESS

A 54 year-old male with medical history remarkable for Graves' disease (x 6 years, controlled on methimazole therapy), systolic (EF 10%) and diastolic cardiomyopathy presents from outside hospital with worsening dyspnea and vomiting.

PAST MEDICAL HISTORY

Graves' Disease (2008) methimazole 2.5 mg daily, last titrated down ~2 weeks ago

- In the setting of growing goiter, presented with heart failure, in a "thyroid storm"
- Declined surgical or iodine ablation therapies
- Has never been in a drug-free remission

- **Systolic and diastolic heart failure** (EF 10%), +Bi-v-ICD aspirin 81 mg; furosemide 20 mg daily
  - Feels "toxic" on ACEI and BB so does not take them

Atrial fibrillation (CHADS2 = 1) **+ SVT** s/p cardioversion and ablation

Anxiety

PERTINENT HISTORY

Family history

- Brother with hypothyroidism

Social history

- On disability; previously worked as an electrical engineer and in welding
- Lives with parents
- Rare etoh, formerly drank "heavily" in intermittent binges
- 35-pack year smoking history; quit 2013

REVIEW OF SYSTEMS

Constitutional: Denies fevers, chills, night sweats, weight changes, hot or cold intolerance. Fatigue
HEENT: Headaches. Denies vision changes, difficulty swallowing, hoarseness, or enlargement of thyroid.
Cardiovascular: Denies chest pain, palpitations, syncope. Bilateral LE edema, dyspnea at rest and with exertion, orthopnea.
Respiratory: Patient denies wheezing. Cough.
Gastrointestinal: Denies abdominal pain, nausea, vomiting, change in appetite, diarrhea. Constipation. No change in color of stool.
Genitourinary: Denies urinary frequency or urgency. No change in color of urine or hematuria.
Skin: Denies excessive moisture, dryness to skin. No rashes.
Musculoskeletal: Denies myalgias, arthralgias, joint swelling.
Neurological: Denies weakness, numbness, tingling. Tremors.
Psychiatric: Denies depression or anxiety.

PHYSICAL EXAMINATION

BP 106/74 **P** 96 **T** 36.3 (97.3) **R** 20 **O2** 97% RA **BMI** 26.45

General: Patient is in mild acute distress, alert, oriented.
HEENT: EOMI. Mild scleral icterus. No peri-orbital edema, chemosis, or injections noted.
Neck: Supple, thyroid is symmetric, with no palpable nodules or thyromegaly. JVD is present to ~8cm.
Cardiovascular: Regular rhythm, tachycardic, without murmurs or gallops
Pulmonary: Good respiratory effort. Bibasilar rales to mid-lung.
Abdomen: Abdomen is distended, soft, non-tender. No hepatomegaly.
Musculoskeletal: Moving all extremities. 2+ bilateral pitting edema to knee.
Neurological: A/O x 3. Strength 5/5, sensation intact. No tremors.
Skin: Warm, dry, no xerosis or excessive oiliness. Diaphoretic, Mild jaundice.
Psychiatric: Cooperative, slightly anxious affect.

DIAGNOSTIC EVALUATION

Glucose	144
Sodium	136
Potassium	4.0
Chloride	97
CO2	25
Anion Gap	14
BUN	44
Creatinine	1.8
GFR	40
Calcium	8.6
Albumin	3.5
Total Protein	7.0
T bili	2.4
C bili	1.4
U bili	1.0
Alk Phos	136
AST	388
ALT	577

WBC	7.7
HGB	16.7
HCT	48.8
PLT	173

TSH	7.07
Free T4	1.28
T3	83

Anti-TPO	29.0
Anti-TG	1.9
TSI	1.1

RECENT BASELINE STUDIES

	2/13	2/24	2/25	2/26	2/27	2/28
Glucose						144
Sodium		123	131	132	137	136
Potassium		5.9	5.0	4.4	3.4	4.0
Chloride		93	96	94	97	97
CO2		21	18	23	27	25
BUN		41	45	52	49	44
Creatinine		1.4	1.4	1.6	1.4	1.8
Calcium		9.1				8.6
Albumin		4.1	3.4	3.6	3.0	3.5
Total Protein		7.5				7.0
T bili	1.7	4.4				2.4
C bili	0.7					1.4
U bili						1.0
Alk Phos			108	116	123	136
AST	24	185	845	856	408	388
ALT	23	253	608	775	566	577

	1/19	2/13	2/25	2/28
TSH	4.43	6.28	5.39	7.07
Free T4		1.33	1.22	1.28
T3				83

CARDIAC EVALUATION

Chest X-Ray	Cardiomegaly, engorged pulmonary vasculature with cephalization, interstitial thickening with increased opacification in R lower lung field c/w consolidation vs. worsened edema, blurred border of R hemidiaphragm and loss on lateral view suggestive of R-sided pleural effusion

Cardiac Enzymes	**Negative**

ECHO	LV severely dilated LV EF 10.7% LV thrombus in apex Moderate tricuspid regurgitation Moderate mitral regurgitation RV performance moderately reduced There is no pericardial effusion.

Coronary Catheterization	No evidence of CAD. Elevated right-sided hemodynamics. Significant improvement in systemic pressure and cardiac output on dobutamine

WHAT WOULD YOU DO?

At this time, the Endocrine service is consulted to comment on whether methimazole could be contributing to the abnormal liver function tests and whether it should be stopped.

Drug-Induced Hepatotoxicity – A Diagnosis of Exclusion

- Ideal criteria:
  - Histological confirmation of hepatocellular injury and re-challenge
- Practical criteria:
  - Clinical and laboratory evidence of hepatocellular dysfunction
  - Onset of symptoms temporally related to drug therapy
  - No serologic evidence for current infection with hepatitis, CMV, or EBV
  - Absence of acute hepatic insult such as shock or sepsis
  - No evidence of concomitantly admnistered drugs that are known hepatotoxins

Hanson JS. Propylthiouracil and hepatitis: two cases and a review of the literature. Arch Intern Med. 1984;144:994-996.

DIAGNOSTIC EVALUATION

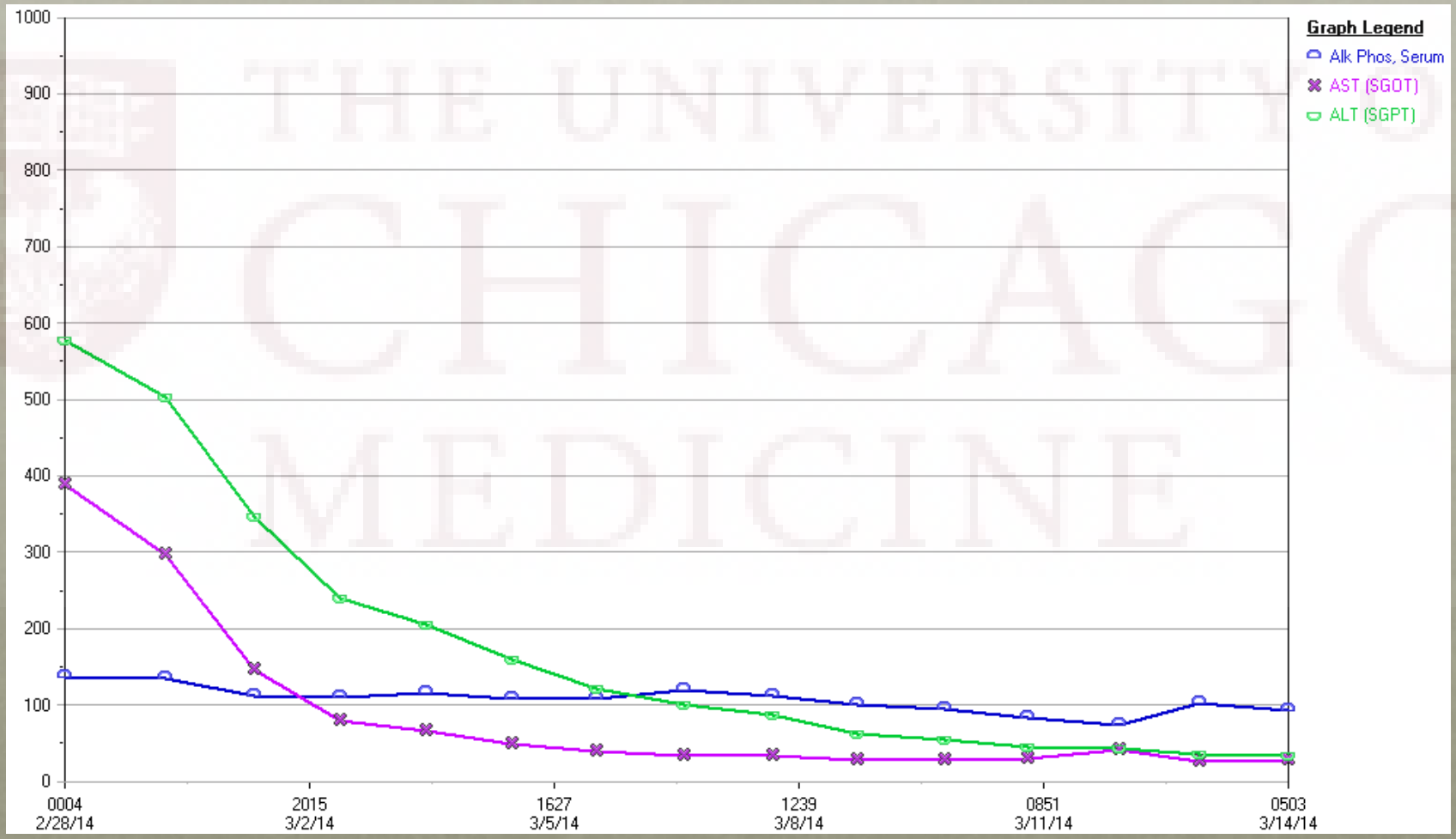
Cholestasis due to hyperthyroidism?
Unlikely in presence of normal thyroid hormone levels

Ferritin	83.3
Ceruloplasmin	37.9 (15-30)
Acute hepatitis panel	Negative
EBV	IGG+, IGM-

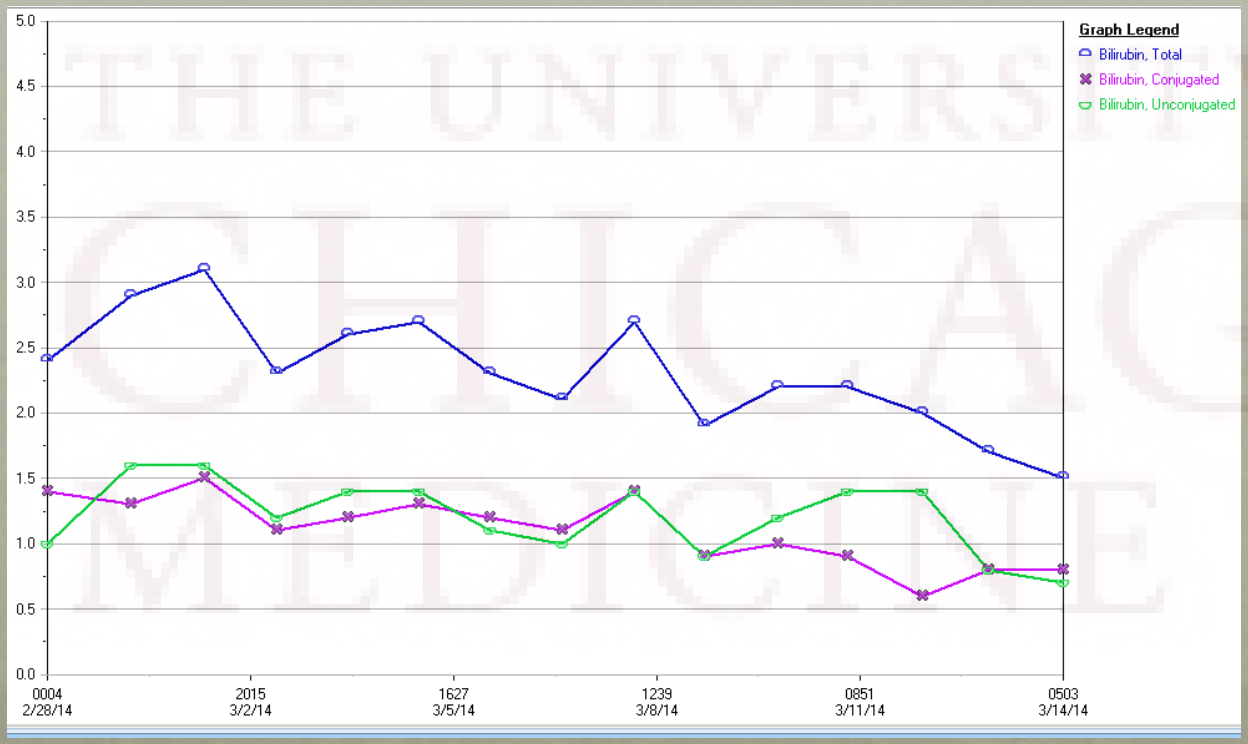
Lactic Dehydrogebase	720 U/L (116-245)
Haptoglobin	84 mg/dL (51-192)

Abdominal ultrasound with dopplers	Normal doppler duplex eval of hepatic vasculature with no sonographic evidence of Budd-Chiari
Gallbladder ultrasound	Diffuse gallbladder wall thickening and biliary sludge, no secondary signs to suggest acute cholecystitis. Trace peri-hepatic ascites and small right pleural effusions
Abdominal ultrasound (repeated here)	midly echogenic liver; nonspecific gallbladder wall thickening with sludge and no gross stones.

ASSESSMENT OF LIVER FUNCTION



ASSESSMENT OF LIVER FUNCTION



Endocr (2010) 38:24–28

Table 1 Side effect of antithyroid drugs

Side effect	Frequency
Skin reactions	4–6%
Arthralgias	1–5%
Gastrointestinal effects	1–5%
Polyarthritis	1–2%
Agranulocytosis	0.1–0.5%
Hepatitis	0.1–0.2%
Abnormal sense of taste or smell	Rare
ANCA–positive vasculitis	Rare
Cholestasis	Rare
Hypoprothrombinemia	Rare
Hypoglycemia	Rare
Other hematologic effects	Very rare
Pancreatitis	Very rare
Sialadenitis	Very rare

HISTOLOGICAL EVALUATION

- Histological confirmation of hepatocellular injury and drug re-challenge can help to re-establish the diagnosis.
- 1/3 of patients taking PTU develop transient increases in transaminase concentrations – which may be associated with focal hepatic necrosis on liver biopsy.

Liaw YF, et al. Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. A cohort study. Ann Intern Med. 1993;118(6):424.

Mikhail N. Methimazole induced cholestatic jaundice. South Med J. 2004;97:178-182.

Table 1. Previously reported cases of jaundice induced by methimazole

Reference	Age/Sex	Dose	Latent period*	Recovery period†	Comments
4	67/F	10 mg tid	29 days	-	Fatal agranulocytosis
5	62/F	5 mg tid	3 wk	9 days	Agranulocytosis
6	63/F	15 mg qid	7 wk	10 wk	Agranulocytosis
7	38/F	20 mg/day	27 days	6 mo	
8	36/F	15 qid	25 days	8 wk	
9	54/F	40 mg/day	25 days	-	Fatal pneumonia
10	74/F	10 qid	12 days	2 mo	
11	75/F	10 mg qid	20 days	100 days	Methimazole continued
	62/F	10 mg qid	5 wk	1 mo	
12	58/F	20 mg/day	18 days	5 days	Rechallenge
13	48/F	10 mg tid	2 wk	3 mo	
14	68/M	20 mg tid	9 wk	3 mo	

**Time elapsed from the beginning of treatment with methimazole until development of icterus or hyperbilirubinemia.*

†Time taken for serum bilirubin levels to normalize after discontinuing methimazole therapy.

Table 2. Previously reported cases of jaundice induced by carbimazole

Reference	Age/Sex	Dose	Latent period[a]	Recovery period[b]	Comments
15	64/M	40 mg/day	81 days	5 days	LTT
16	24/F	40 mg/day	3 mo	"Rapid"	Rechallenge
17	81/F	30 mg/day	6 wk	5 days	Rechallenge, LTT
18	45/F	20 mg/day	10 days	15 days	Rechallenge
19	57/F	40 mg/day	6 wk	-	Fulminant hepatitis
20	72/F	30 mg/day	5 wk	NR	Hyperesinophilia
21	70/F	30 mg/day	2 days	3 mo	Jaundice occurred on second drug exposure
22	59/M	60 mg/day	8 days	15 days	

[a]Time elapsed from the beginning of treatment with carbimazole until development of icterus or hyperbilirubinemia.

[b]Time taken for serum bilirubin levels to normalize after discontinuing carbimazole therapy.

LTT = lymphocyte transformation test.

NR = not reported.

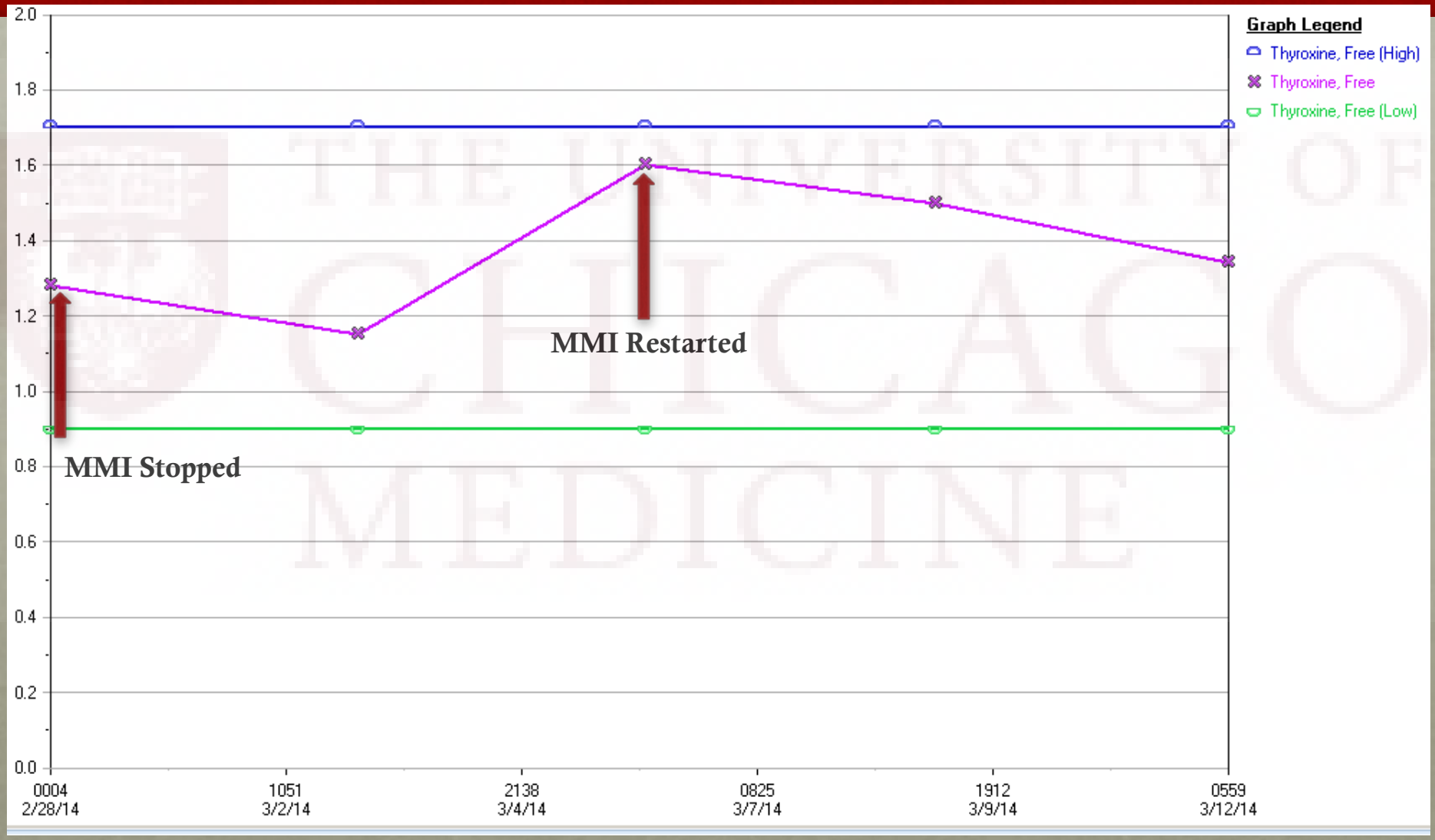
Mazokopakis EE, et al. Carbimazole-induced acute cholestatic hepatitis. Endocrinologist. 2007;17:127-130.

TABLE 1. Reported Cases of Carbimazole-Induced Cholestatic Liver Disease in the Literature

Report	Age/Sex	Dose	Latent Period*	Comments
Prost et al, 1973[18]	64/M	40 mg/d	81 d	LTT
Jenkins and Evans, 1981[19]	47/F	40 mg/d	10 d	
Efstratiadis et al, 1982[20]	33/M	30 mg/d for 8 d and after 20 mg/d	24 d	
Dinsmore et al, 1983[21]	24/F	40 mg/d	3 mo	Rechallenge
Blom et al, 1985[22]	81/F	30 mg/d	6 wk	Rechallenge, LTT
Wheeler et al, 1985[23]	62/M	45 mg/d	5 wk	
Ayensa et al, 1986[24]	45/F	20 mg/d	10 d	Rechallenge
Cales et al, 1987[25]	72/F	30 mg/d	5 wk	Hypereosinophilia
Ozenne et al, 1989[26]	70/F	30 mg/d	2 d	Jaundice occurred on second drug exposure
Moreno Sanchez et al, 1989[27]	66/F	80 mg/d	2 mo	
Sadoul et al, 1993[28]	59/M	60 mg/d	8 d	
Epeirier et al, 1996[17]	57/F	40 mg/d	6 wk	Fulminant hepatitis
Marazuela et al 2002[29]	33/F	45 mg/d	1 mo	Acute pancreatitis, erythema nodosum
Chan et al, 2003[4]	36/M	30 mg/d	4 wk	Sequential carbimazole and propylthiouracil treatment, death
This report, 2006	45/M	30 mg/d	1 mo	

F indicates female; LTT, lymphocyte transformation test; M, male.
*Time elapsed from the beginning of treatment with carbimazole until development cholestatic liver disease.

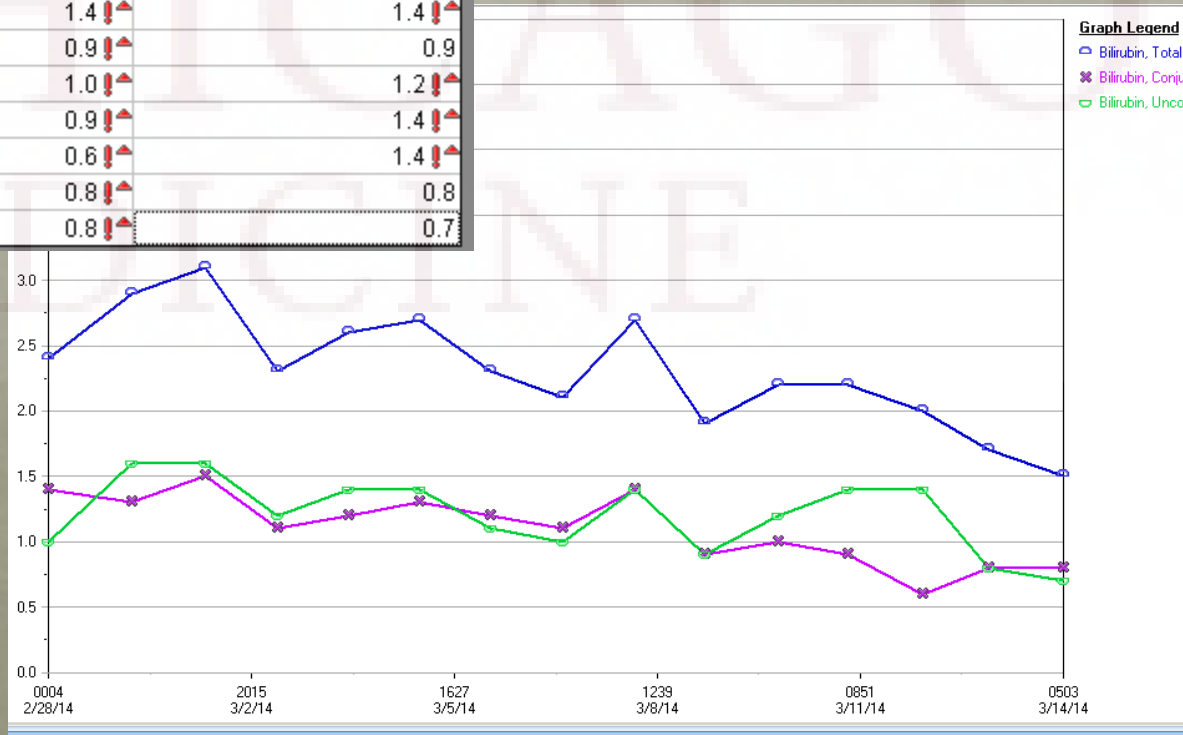
FREE T4


Graph Legend
Thyroxine, Free (High)
Thyroxine, Free
Thyroxine, Free (Low)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
MMI Stopped
MMI Restarted
0004
2/28/14
1051
3/2/14
2138
3/4/14
0825
3/7/14
1912
3/9/14
0559
3/12/14

ASSESSMENT OF LIVER FUNCTION

Flowsheet

	Bilirubin, Total	Bilirubin, Conjugated	Bilirubin, Unconjugated
Ref. Range	Latest Range: 0.1-1.0 mg/dL	Latest Range: 0.0-0.3 mg/dL	Latest Range: 0.1-1.0 mg/dL
2/28/2014 0004	2.4	1.4	1.0
3/1/2014 0405	2.9	1.3	1.6
3/2/2014 0440	3.1	1.5	1.6
3/3/2014 0450	2.3	1.1	1.2
3/4/2014 0445	2.6	1.2	1.4
3/5/2014 0436	2.7	1.3	1.4
3/6/2014 0422	2.3	1.2	1.1
3/7/2014 0446	2.1	1.1	1.0
3/8/2014 0513	2.7	1.4	1.4
3/9/2014 0445	1.9	0.9	0.9
3/10/2014 0522	2.2	1.0	1.2
3/11/2014 0433	2.2	0.9	1.4
3/12/2014 0559	2.0	0.6	1.4
3/13/2014 0411	1.7	0.8	0.8
3/14/2014 0503	1.5	0.8	0.7



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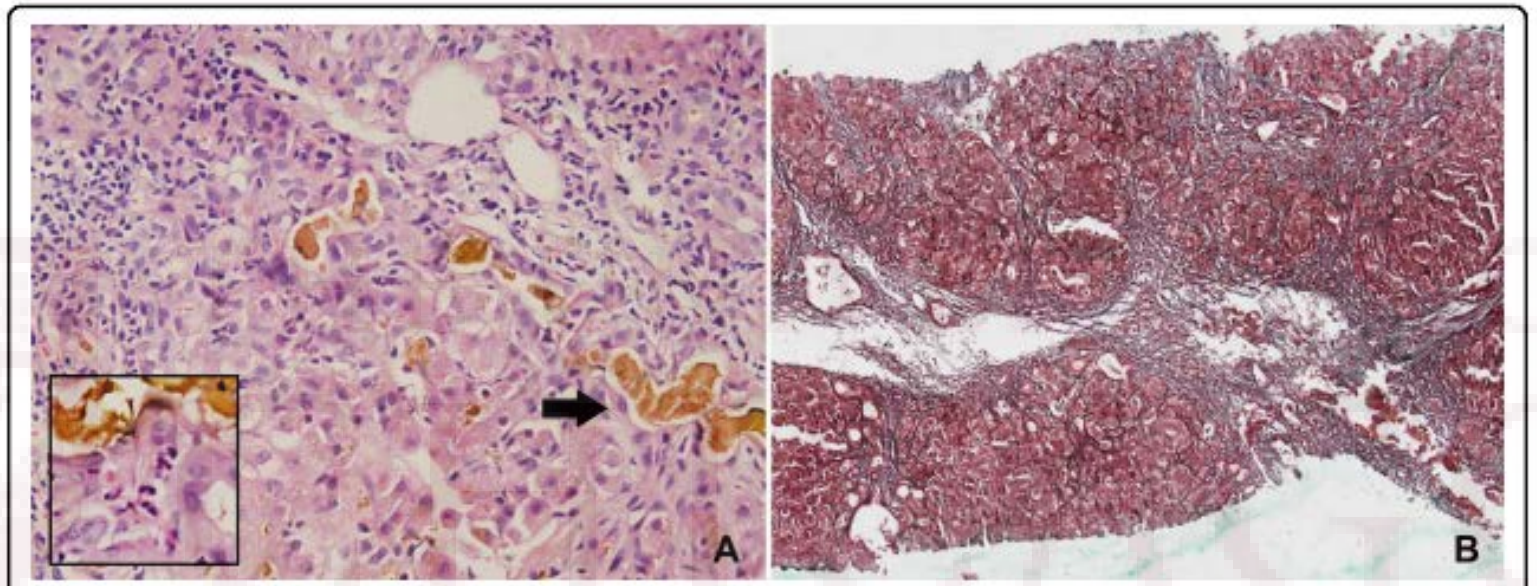
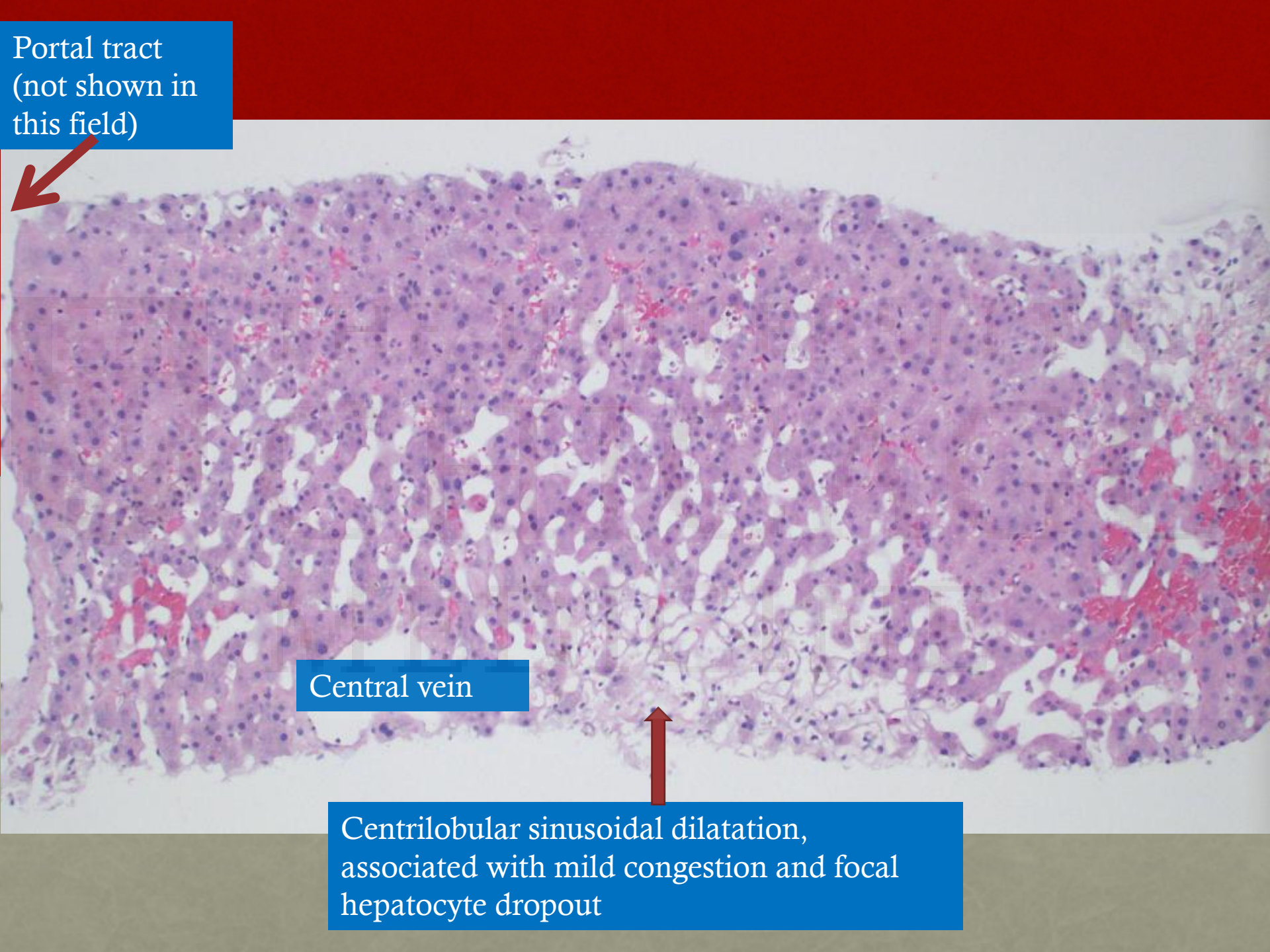


Figure 3 Histological findings of the liver specimen. A: Liver biopsy showing intracanalicular bile plugs (black arrow) and enlarged hepatocytes with feathery degeneration, indicative of intrahepatic cholestasis. Moderate inflammatory infiltration, composed of lymphocytes, neutrophils, as well as eosinophils (inset), was presented in portal area (Hematoxylin and Eosin staining, ×400). B: Expanded portal tracts accompanied by significant hepatic fibrosis (Masson Tri-chrome staining, ×100).

Liver Biopsy in 17/20 patients

Majority had intrahepatic cholestasis

Severe inflammation and hepatic necrosis in only 1 patient


Portal tract (not shown in this field)
Central vein
Centrilobular sinusoidal dilatation, associated with mild congestion and focal hepatocyte dropout

METHIMAZOLE HEPATOTOXICITY

- Severe cholestatic jaundice is rare, and most often occurs within the first 3 months of use, though it may be idiosyncratic (Ogbonna, Mazokopakis, Mikhail).
- Thought to be medicated by an allergic reation.
- Drug reaction seems to be dose-dependent.
- 2010

CONFLICTING DATA

AGE OF ONSET	
"Predisposition for women younger than 30 years of age"	Malik R, Hodgson H. The relationship between the thyroid gland and the liver. QJM. 2002;95:559-569.
Case series – Methimazole 20 patients → Mean age 58.9 years	Mikhail N. Methimazole induced cholestatic jaundice. South Med J. 2004;97:178-182.)
Case series - Carbimazole 15 patients → Mean age 52.9 years	Mazokopakis EE, et al. Carbimazole-induced acute cholestatic hepatitis.

CONFLICTING DATA

Recovery from drug insult	
"Complete, slow recovery is the rule after drug discontinuation."	Livadas S, et al. Liver failure due to antithyroid drugs: report of a case and literature review. Endocr. 2010;38:24-8.
	Eperirier JM, et al. Fulminant hepatitis after carbimazole and propranolol administration. Eur J Gastroenterol Hepatol. 1996;8:287-88.
	Blom H, et al. A case of carbimazole-induced intrahepatic cholestasis. An immune-mediated reaction. Arch Intern Med. 1985;145:1513-15.