3. Vierling JM. Primary biliary cirrhosis and autoimmune cholangiopathy. *Clin Liver Dis.* 2004;8:177-194.
4. Michieletti P, Wanless IR, Katz A, et al. Antimitochondrial antibody–negative primary biliary cirrhosis: a distinct syndrome of autoimmune cholangitis. *Gut.* 1994;35:260-265.
5. Brunner G, Klinge O. A chronic destructive non-supporative cholangitis-like disease picture with antinuclear antibodies (immunocholangitis) [in German]. *Dtsch Med Wochenschr.* 1987;112:1454-1458.
6. Washington MK. Autoimmune liver disease: overlap and outliers. *Mod Pathol.* 2007;20(suppl 1):S15-S30.
7. Chazouillères O, Wendum D, Serfaty L, Rosmorduc O, Poupon R. Long-term outcome and response to therapy of primary biliary cirrhosis–autoimmune hepatitis overlap syndrome. *J Hepatol.* 2006;44:400-406.
8. Cui B, Abe M, Hidata S, et al. Autoimmune hepatitis associated with Graves' disease. *Intern Med.* 2003;42:331-335.
9. Soysal D, Tatar E, Solmaz S, et al. A case of severe cholestatic jaundice associated with Graves' disease. *Turk J Gastroenterol.* 2008;19:77-79.
10. Gallelli L, Staltari O, Palleria C, De Sarro G, Ferraro M. Hepatotoxicity induced by methimazole in a previously healthy patient. *Curr Drug Saf.* 2009;4:204-206.

Review

Hepatic Dysfunction in Hyperthyroidism

Saro Khemichian, MD

Tse-Ling Fong, MD

Division of Gastrointestinal and Liver Diseases
Department of Medicine
Keck School of Medicine
University of Southern California
Los Angeles, California

Hyperthyroidism can affect multiple organ systems, including the cardiovascular, nervous, gastrointestinal, and hepatic systems. The interaction between the thyroid and liver is critical for maintaining homeostasis in both sites. Thyroid hormones are glucuronidated and sulfated within the liver and subsequently excreted into bile; in addition, these hormones maintain the metabolism of bilirubin by playing a role in the enzymatic activity of glucuronyltransferase and by regulating the level of ligandin, a major organic anion-binding protein.[1] Therefore, it is not surprising that hepatic dysfunction is commonly observed in patients with thyroid disease. In 1874, Habershon described a patient with exophthalmic goiter, heart disease, and jaundice who died.[2] Many subsequent case reports and series have highlighted the prevalence of liver test abnormalities (ranging from 15% to 76%) in the setting of hyperthyroidism.[3,4] There are several mechanisms of liver dysfunction in the setting of hyperthyroidism, including liver abnormalities due to hyperthyroidism alone, liver damage related to heart failure and hyperthyroidism, and concomitant liver disease in the setting of hyperthyroidism.

In our hyperthyroidism and liver dysfunction case series, patients were categorized into 3 groups: patients without heart failure, patients with heart failure, and patients without heart failure who had concomitant liver disease.[3] In patients without heart failure, liver dysfunction ranged from mild liver test abnormalities to deep jaundice. This range of liver dysfunction is consistent with other cases reported in the literature.[4-7] However, no studies have demonstrated a correlation between abnormal liver biochemical tests and thyroid hormone levels. Studies monitoring treatment of hyperthyroidism have noted that improvement in a patient's thyroid function is accompanied by normalization of the liver panel. The mechanism of liver injury in pure hyperthyroid states is not well understood. Recently, Upadhyay and colleagues used in vivo and in vitro models to show that excess T3 induces apoptosis of hepatocytes and causes liver dysfunction through activation of the mitochondrial-dependent pathway.[8] In most cases of hyperthyroidism and liver dysfunction without heart failure, liver histology demonstrates some degree of fatty infiltration, cytoplasmic vacuolization, nuclear irregularity, and hyperchromatism in hepatocytes.[8] Functional changes in mitochondria (such as enlargement) and formation of megamitochondria have been reported in the livers of hyperthyroid patients and in a rat model of hyperthyroidism.[9,10]

Hyperthyroid patients with heart failure in our series were more likely to manifest more severe liver dysfunction

Address correspondence to:
Dr. Tse-Ling Fong, Division of Gastrointestinal and Liver Diseases, Department of Medicine, Keck School of Medicine, University of Southern California, 1510 San Pablo Street, 2/F, Los Angeles, CA 90033; Tel: 323-442-5908; Fax: 323-442-6169.

with respect to deep jaundice (mean, 5.3 mg/dL; highest, 24 mg/dL), coagulopathy, hepatomegaly, and even ascites, compared to patients without heart failure.[3] Heart failure resulting in hepatic congestion—even in the absence of hyperthyroidism—is often associated with protean liver test abnormalities, including acute hepatocellular injury, hyperbilirubinemia, and coagulopathy.[11] In particular, right-sided heart failure can result in passive congestion of the liver usually referred to as "congestive hepatopathy." Decreased cardiac output may also result in decreased hepatic blood flow and arterial oxygen saturation. These processes are intertwined, and clear distinctions may not be possible.[12] The liver is often enlarged and pulsatile in patients with congestive hepatopathy. Ascites is common due to enlargement of sinusoidal fenestrae secondary to sinusoidal congestion and exudation of protein-rich fluid into the space of Disse, which subsequently overwhelms the lymphatic vessels.[13] Myers and colleagues assessed the clinical, hemodynamic, and histologic data of 83 patients with congestive hepatopathy; mild abnormalities in liver enzymes and bilirubin levels were noted in most patients.[11] However, aminotransferase levels may be higher than 2,000 IU/L in the setting of acute cardiac dysfunction, and patients may have profound jaundice along with coagulopathy.[11]

Hyperthyroidism, particularly Graves disease, can also be associated with other liver conditions. Up to 10% of patients with Graves disease have a coexisting autoimmune disorder.[14] The association between Graves disease and primary biliary cirrhosis (PBC) or autoimmune hepatitis is well described in the literature. Conversely, Graves disease is a common concurrent autoimmune condition associated with various chronic liver diseases.[15]

The case reported by Venkat and colleagues—which describes a patient with Graves disease, heart failure, jaundice, and positive autoimmune markers—illustrates the challenges of discerning the cause of liver dysfunction in this setting.[16] The clinical presentation of this patient was very similar to that of our own patients. However, this case study is the first reported case of Graves disease coexisting with autoimmune cholangiopathy (AIC). Originally referred to as "immunocholangitis" by Brunner and Klinge, AIC is an antimitochondrial antibody (AMA)-negative and antinuclear antibody (ANA)-positive condition; otherwise, AIC shares the typical clinical and histologic features of PBC.[17] Mitochondrial antigen has been shown to be expressed on the apical membranes of biliary epithelial cells from AMA-negative as well as AMA-positive PBC patients, suggesting that the pathogenesis of both conditions is very similar.[18] Michieletti and associates compared 17 AIC patients with 17 PBC patients and found that both conditions had a predilection for women and an association with hypothyroidism.[19] Liver tests were characterized by high alkaline phosphatase levels (mean, 500 U/L). In the patient treated by Venkat and coworkers, histopathologic findings were consistent with AIC, although the alkaline phosphatase level was not as elevated as in a typical AIC patient.[16] The presence of a high ANA value and a negative AMA titer is also consistent with AIC. The interpretation of autoimmune markers in Graves disease should take into consideration the high prevalence of nonthyroid autoantibodies, particularly ANA.[20-22]

In conclusion, it is apparent that the thyroid and liver are intertwined in many ways. A vigilant effort should be undertaken to diagnose the liver condition of patients who present with hyperthyroidism and liver dysfunction—as in the case report by Venkat and associates—so that appropriate therapy can be promptly initiated.

References

1. Fagiuoli S, Van Thiel DH. The liver in endocrine disorders. In: Rustgi VK, Van Thiel DH, eds. *The Liver in Systemic Disease*. New York, New York: Raven Press; 1993:285-287.
2. Habershon SO. Exophthalmic goiter, heart disease, jaundice: death. *Lancet.* 1874;1:510-512.
3. Fong TL, McHutchison JG, Reynolds TB. Hyperthyroidism and hepatic dysfunction. A case series analysis. *J Clin Gastroenterol.* 1992;14:240-244.
4. Huang MJ, Li KL, Wei JS, Wu SS, Fan KD, Liaw YF. Sequential liver and bone biochemical changes in hyperthyroidism: prospective controlled follow-up study. *Am J Gastroenterol.* 1994;89:1071-1076.
5. Kubota S, Amino N, Matsumoto Y, et al. Serial changes in liver function tests in patients with thyrotoxicosis induced by Graves' disease and painless thyroiditis. *Thyroid.* 2008;18:283-287.
6. Hull K, Horenstein R, Naglieri R, Munir K, Ghany M, Celi FS. Two cases of thyroid storm–associated cholestatic jaundice. *Endocr Pract.* 2007;13:476-480.
7. Barnes SC, Wicking JM, Johnston JD. Graves' disease presenting with cholestatic jaundice. *Ann Clin Biochem.* 1999;36:677-679.
8. Upadhyay G, Singh R, Kumar A, Kumar S, Kapoor A, Godbole MM. Severe hyperthyroidism induces mitochondria-mediated apoptosis in rat liver. *Hepatology.* 2004;39:1120-1130.
9. Klion FM, Segal R, Schaffner F. The effect of altered thyroid function on the ultrastructure of the human liver. *Am J Med.* 1971;50:317-324.
10. Kalderon B, Hermesh O, Bar-Tana J. Mitochondrial permeability transition is induced by in vivo thyroid hormone treatment. *Endocrinology.* 1995;136:3552-3556.
11. Myers RP, Cerini R, Sayegh R, et al. Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. *Hepatology.* 2003;37:393-400.
12. Giallourakis CC, Rosenberg PM, Friedman LS. The liver in heart failure. *Clin Liver Dis.* 2002;6:947-967, viii-ix.
13. Runyon BA. Cardiac ascites: a characterization. *J Clin Gastroenterol.* 1988;10:410-412.
14. Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med.* 2010;123:183.e1-183.e9.
15. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Genetic predispositions for the immunological features of chronic active hepatitis. *Hepatology.* 1993;18:816-822.
16. Venkat D, Wirtz D, Patel T. Autoimmune cholangiopathy and high-output heart failure in a patient with Graves disease. *Gastroenterol Hepatol (N Y).* 2011;7:334-337.
17. Vierling JM. Primary biliary cirrhosis and autoimmune cholangiopathy. *Clin Liver Dis.* 2004;8:177-194.

18. Tsuneyama K, Van De Water J, Van Thiel D, et al. Abnormal expression of PDC-E2 on the apical surface of biliary epithelial cells in patients with anti-mitochondrial antibody–negative primary biliary cirrhosis. *Hepatology.* 1995;22: 1440-1446.
19. Michieletti P, Wanless IR, Katz A, et al. Antimitochondrial antibody–negative primary biliary cirrhosis: a distinct syndrome of autoimmune cholangitis. *Gut.* 1994;35:260-265.
20. Baethge BA, Levine SN, Wolf RE. Antibodies to nuclear antigens in Graves' disease. *J Clin Endocrinol Metab.* 1988;66:485-488.
21. Morita S, Arima T, Matsuda M. Prevalence of nonthyroid-specific auto-antibodies in autoimmune thyroid diseases. *J Clin Endocrinol Metab.* 1995;80: 1203-1206.
22. Petri M, Karlson EW, Cooper DS, Ladenson PW. Autoantibody tests in auto-immune thyroid disease: a case-control study. *J Rheumatol.* 1991;18:1529-1531.