Digestive Diseases and Sciences, Vol. 50, No. 1 (January 2005), pp. 207–211 (© 2005)
DOI: 10.1007/s10620-005-1302-0

CASE REPORT

Autoimmune Hepatitis and Thyroiditis Associated with Rifampin and Pyrazinamide Prophylaxis: An Unusual Reaction

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KEY WORDS: autoimmune hepatitis; autoimmune thyroiditis; rifampin prophylaxis; pyrazinamide prophylaxis.

Drug-induced autoimmune hepatitis (DIAH) and thyroiditis with rifampin and pyrazinamide has not been reported to our knowledge. We report on a 25-year-old male who presented with signs of acute anicteric hepatitis and subclinical thyroiditis 3 weeks after starting antituberculosis (anti-TB) prophylaxis. After discontinuation of the rifampin and pyrazinamide prophylaxis, his symptoms of hepatitis resolved, and liver enzymes and thyroid tests returned to normal after several months. Since neither rifampin nor pyrazinamide has been described so far as a triggering factor for autoimmune hepatitis and thyroiditis, the case is discussed and the literature reviewed.

CASE REPORT

A 25-year-old man in otherwise excellent health presented 3 weeks after the start of anti-TB prophylaxis. He was found to have a positive purified protein derivative (PPD) in May 2002 that was performed as part of a routine employment physical examination. A PPD 2 years earlier had been negative. He was unable to recall any exposure to TB, but he was a medical student at an urban medical center. A chest x-ray taken after the PPD was found to be unremarkable. The patient chose not to start anti-TB prophylaxis at this time, as he was asymptomatic. However, in October 2002, he was convinced to start a 2-month regimen of rifampin and pyrazinamide prophylaxis, which was the guideline at that time for treatment of latent TB (1). Three weeks after beginning prophylaxis, he presented with anorexia, fever, fatigue, and right upper quadrant pain. Physical examination was unremarkable except for mild right upper quadrant tenderness on deep palpation. No organomegaly or tenderness was noted. No skin eruption was present. The patient was a nonsmoker, but did consume alcohol, up to two six-packs of beer on the weekends. He had no other comorbid conditions. Aminotransferases at presentation were elevated, with an ALT of 749 IU/L (normal, 0–40 IU/L) and an AST of 938 IU/L (normal, 0–40 IU/L). Preprophylaxis baseline ALT and AST had been normal (12 and 22 IU/L, respectively). Serum total protein was 6.7 g/dL (normal, 6.0–8.5 g/dL), serum albumin was 3.8 g/dL (normal, 3.5–5.0 g/dL), and serum globulin was 2.9 g/dL (1.5–3.0 g/dL). Blood work also revealed an eosinophil count of 15%. Serological studies showed a positive antinuclear antibody (ANA) of >1:640 in a speckled pattern. Anti–smooth muscle antibody (ASMA) was elevated, at 1:80. Tests for acute and chronic viral infection, including hepatitis A, B, and C, mononucleosis, and cytomegalovirus, were all negative. Iron and copper studies were normal, and an abdominal ultrasound was unremarkable with normal echogenicity of the liver. One week after discontinuation of rifampin and pyrazinamide, the ALT was further elevated, to 1256 IU/L, and AST was 695 IU/L. INR was slightly prolonged, at 1.4 (normal, 0.9–1.1), but the bilirubin level was normal at 0.4 mg/dL (normal, 0.1–1.0 mg/dL). No liver biopsy was performed, as the enzymes slowly declined back into the normal range over the next 5 months.

The patient presented again in March 2003 with continued mild right upper quadrant discomfort. His review of systems revealed a normal appetite, with no palpitations, insomnia, diarrhea, weight loss, or heat intolerance. Physical examination showed a well-developed and well-nourished male, standing 6 feet 1 in. and weighing 174 lb. His blood pressure was 112/72, and his pulse was 64. He was nonicteric with a clear oropharynx. Chest and cardiac exam were unremarkable. The abdomen was scaphoid with no organomegaly or masses. The patient complained of slight tenderness upon deep palpation in the renal flank areas bilaterally. There was no clubbing, edema, or palmar erythema. Laboratory testing showed an ALT of 15 IU/L and AST of 22 IU/L. The ANA was still 1:640, and ASMA was 1:40. Anti–liver kidney muscle (LKM) antibody was negative. Both total protein and albumin were normal (6.4 and 4.0 g/dL, respectively). However, the TSH was very low, at 0.03 μIU/L (normal, 0.5–5.5 μIU/L); total T3 was mildly elevated, at 179.12 ng/dL (normal, 87–178 ng/dL); T4 was 8.9 μg/dL (normal, 6.09–12.23 μg/dL); and free T4 was

Manuscript received February 17, 2004; accepted April 10, 2004.

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TABLE 1. DRUGS REPORTED TO CAUSE AUTOIMMUNE HEPATITIS

Drug [Ref. No.]*	*No. of cases*	*ANA*	*ASMA*	*Other autoimmune Phenomena*
Methyldopa [6–8]	Multiple	+ (16%)	+ (35%)	Antierythrocyte
Nitrofurantoin [9–14]	Multiple	+ (80%)	+ (72%)	
Minocycline [15–21]	Multiple	+	−	Anti-DNA
Clometacin [22,23]†	Multiple	−	+	Anti-DNA
Interferon [24–27]	Multiple	+	+	Antierythrocyte, antimicrosomal
Oxyphenisatin [27–31]‡	Multiple	+ (67%)	+ (67%)	
Papaverine [41–44]	IR	+	+	
Atorvastatin [45,46]	IR	+	+	
Germander [47,48]	IR	+	+	
Propylthiouracil [49–52]	IR	+	+	
Diclofenac [53,54]	IR	+	−	
Pemoline [55]	IR	+	−	Antimicrosomal
Doxycycline [56]	IR	+	−	
Benzarone [57]	IR	−	+	
Fenofibrate [58]	−	−		
Dai-saiko-to (herb) [59]	IR	+	+	

Note. ANA, anti-nuclear antibody; ASMA, anti–smooth muscle antibody; IR, isolated reports.
*Selected references are given.
†No longer in use.
‡Not available in the United States.

1.51 ng/dL (normal, 1.6–3.7 ng/dL). The antithyroid and antithyroglobulin antibodies were both elevated, at 339.7 IU/mL (normal, <2.0 IU/mL) and 4 IU/mL (normal, <2 IU/mL). An endocrinology consultation was obtained at this time. Eye exam was normal, with no lid lag or proptosis. The thyroid gland was at the upper limit of normal size (approximately 25 g) and nontender. Reflexes were 3+ and brisk. It was felt that the patient had a subclinical thyroiditis, and he was followed over the course of the next several weeks.

In May 2003, his thyroiditis became more clinically evident, with complaints of a weight loss of 10 lb despite increased appetite, palpitations, and insomnia. Laboratory testing showed a further decrease in TSH (0.01 μIU/L), and a thyroid scan revealed decreased uptake, suggesting diffuse thyroiditis. These symptoms resolved without intervention over the next 4 months and, by September 2003, had fully resolved. The ALT and AST values remained normal (14 and 16 IU/L). Laboratory testing in September 2003 revealed an increase in TSH (8.3 mIU/L), but no symptoms of hypothyroidism were reported. The ALT and AST remained normal (10 and 16 IU/L). The ANA and ASMA remained positive at 1:320 and 1:80, respectively. The most recent testing, in December 2003, showed an ALT of 20 IU/L and an AST of 12 IU/L. The TSH level was near normal at 6.5 μIU/L, and the chest x-ray also remained normal. The patient's endocrinologist is currently following him expectantly.

DISCUSSION

Hepatic cellular necrosis from the combination of rifampin and pyrazinamide has been well documented (2, 3). As of 2003, the Centers for Disease Control (CDC) no longer recommends these drugs for TB prophylaxis (4). To our knowledge, this case likely represents the development of acute drug-induced autoimmune hepatitis and thyroiditis secondary to the combination of rifampin and pyrazinamide, which has not been previously reported.

Drug-induced autoimmune hepatitis (DIAH) has been reported for a number of agents (5), the most common of which are currently methyldopa (6–8), nitrofurantoin (9–14), minocycline (15–21), and clometacin (22, 23). Interferon is increasingly being cited as a possible cause (24–27). Oxyphenisatin in no longer in use (27–31). Other drugs associated with autoimmune hepatitis are listed in Table 1. Nearly all of these agents are associated with Type 1 autoimmune hepatitis (presence of antinuclear antibody). The mechanism is believed to be the binding of a drug metabolite to either cellular receptors or P-450 proteins, resulting in antigen formation, which induces attack by the immune system. Human leukocyte antigen (HLA) class II is displayed on hepatocytes, which exposes normal liver cell membrane constituents to antigen-processing cells; the asialoglycoprotein receptor and the cytochrome mono-oxygenase P-450 IID6 are proposed as the triggering autoantigens (32). Some patients appear to be genetically susceptible to DIAH; the condition is associated with the complement allele C4AQO and with HLA haplotypes B8, B14, DR3, DR4, and Dw3. In addition, *C4A* gene deletions are associated with the development of autoimmune hepatitis in younger patients (33). In this patient, we suspect that the combination of the two drugs was responsible for the triggering of the autoimmune process; however, his HLA phenotype was not tested.

Typically, DIAH presents with symptoms of acute liver disease. ALT/AST levels are elevated 5–50× the upper limit of normal, and autoantibodies that are most commonly present are antinuclear, anti–smooth muscle, and anti-liver/kidney/microsomal-1. The prevalence of detectable autoantibodies is variable up to 80% (Table 1).

TABLE 2. DRUGS REPORTED TO CAUSE AUTOIMMUNE THYROIDITIS

Drug [Ref. No.]*	*No. of cases*	*Antimicrosomal*	*Antithyroglobulin*	*Other*
Interferon-α [60–75]	Multiple	+	±	
Lithium [76]	IR	+	+	
Amiodarone [77]	IR	+	−	
Ethosuxamide [78]	IR	+	−	Anti-DNA
Alimemazine [79]†	IR	+	+	

Note. IR, isolated reports.
*Selected references are given.
†Phenothiazine derivative.

Further laboratory testing may show an elevated IgG and mildly elevated serum bilirubin and alkaline phosphatase. This condition has been associated with other autoimmune phenomena, including ulcerative colitis, rheumatoid arthritis, anemia, myopathy, and thyroiditis (34–37). Pertinent to this case, autoimmune thyroiditis has developed in association with DIAH in approximately 8–10% of cases (38, 39). Treatment of DIAH is withdrawal of the offending agent and, if necessary, prednisone and/or azathioprine, if the inflammation fails to recede.

This patient also developed thyroiditis, which we suspect was due to the same or similar mechanisms that induced the autoimmune hepatitis. The patient did not complain of any thyroid-related symptoms at his initial presentation, and physical examination was unremarkable except for mild hyperreflexia. However, over the next several months, his thyroid-stimulating hormone level became progressively lower, and he eventually became symptomatic with transient hyperthyroidism. Serological evidence to support an underlying autoimmune thyroiditis was the presence of antimicrosomal and antithyroglobulin antibodies (40). Other agents implicated in drug-induced autoimmune thyroiditis are summarized in Table 2. We recommend that autoantibodies be tested in any suspected case of drug-induced liver disease associated with these agents to determine the incidence and natural history of such an autoimmune phenomenon.

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