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CASE REPORT

Steroids for the treatment of methimazole-induced severe cholestatic jaundice in a 74-year-old woman with type 2 diabetes

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Abstract Methimazole is a widely used antithyroid agent. Although methimazole is generally well tolerated, rare but severe cholestatic jaundice may occur. We described a 74-year-old woman who had a 10-year history of type 2 diabetes had developed severe jaundice and itching 1 month after receiving methimazole (10 mg tid) and propranolol (10 mg tid) for the treatment of hyperthyroidism. Clinical investigations revealed no evidence of any mechanical obstruction in the common bile duct or other obvious causes of hepatic injury, and the diagnosis methimazole-induced cholestasis was made on the basis of the temporal relationship between initiation of methimazole and onset of cholestasis. Methimazole was hence discontinued. However, the patient experienced a progressive worsening in cholestasis after receiving 2 weeks of ursodeoxycholic acid (UDCA) therapy. Prednisone therapy was then attempted. Liver function tests eventually improved with combination of glucocorticoids and ursodeoxycholic acid therapy. This case clearly showed that glucocorticoids could be a possible additional way of treatment for some cases of drug-induced cholestatic jaundice even in diabetic patients.

Keywords Cholestasis · Methimazole · Glucocorticoids therapy · Diabetes

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Introduction

Methimazole is a widely used antithyroid agent. Cholestatic jaundice is a rare but potentially fatal complication arising from the use of methimazole. The underlying mechanism of pathogenesis is still unclear. However, some studies suggest that it is most likely an allergic reaction [1]. No known effective medical therapy has been found. The most important intervention is prompt withdrawal of the offending drug. We present a case of a 74-year-old woman with type 2 diabetes and Graves' disease, and methimazole-induced severe cholestatic jaundice requiring steroid therapy. She was successfully treated with steroids following combined therapy with ursodeoxycholic acid (UDCA), and tight control of diabetes was maintained with appropriate modifications in insulin dosage.

Case report

A 74-year-old Chinese woman was referred to our endocrine clinic because of persisting jaundice and severe pruritus on March 6, 2009, with appetite decreased. Hyperthyroidism had been diagnosed based on an elevated plasma free thyroxine (FT4) level of 79.1 (normal, 12.0–22 pmol/l), free triiodothyronine (FT3) uptake of 25.8 (normal, 3.1–6.8 pmol/l), and thyrotropin level of <0.005 (0.3–4.2 mIU/l) 3 months ago (January 13, 2009). The initial laboratory studies showed an aspartate aminotransferase (AST) value of 22.5 (normal, 0–45 U/l), alanine amniotransferase (ALT) 22.8 (normal, 0–45 U/l), alkaline phosphatase 65.3 (normal, 40–150 U/l), and gamma-glutamyltranspeptidase (γ-GT) level 21.3 (normal, 0–50 U/l), total bilirubin 18.5 (normal, 6–22 μmol/l), and conjugated bilirubin 12.5 (normal, 0–6 μmol/l). Complete blood cell

count and basic chemistry and coagulation test results were all within normal range. Treatment was started with 10 mg of methimazole and 10 mg of propranolol, each three times daily. One month after starting methimazole (January 22, 2009), the patient began to have jaundice and generalized pruritus. She continued taking her medication until she had nausea, anorexia and change in urine and stool color. On admission to the hospital, she had severe icterus of the sclerae and skin. She denied any abdominal pain and fever, had no signs of heart failure.

The patient did have a medical history of type 2 diabetes for 10 years and, was on diet and physical activities to control hyperglycemia for several years and had no anti-diabetic medicine therapy. The patient reported no alcohol use, no occupational exposure to hepatotoxins, or risk factors for hepatitis A, B, and C viruses. She had no history of recreational drugs or travel.

Physical examination revealed that her blood pressure was 130/76 mmHg and her pulse rate was 78 beats per minute. She was noted to be deeply jaundiced, but there were no cutaneous stigmata of liver disease. She had mild hands tremor. Her thyroid was diffusely enlarged. The abdomen was supple without any tenderness; both the liver and spleen were not palpable.

Repeated laboratory test values showed worsening of the patient's liver functions, with a total bilirubin 255.2 μmol/l; the conjugated bilirubin 206.4 μmol/l; AST 48.5 U/l; ALT 92.5 U/l; ALP 301.4 U/l; γ-GT 532.6 U/l; Prothrombin time and partial thromboplastin time values were within normal limits. Serum free T3 and T4 levels turned to be normal at 4.7 and 27 pmol/l, respectively. And serum thyrotropin level was 0.016 mIU/l. Serologic tests for hepatitis A, B, C, and E viruses were all negative. An ultrasonogram of the abdomen showed unremarkable changes of the liver, pancreas, and spleen, without any evidence of biliary dilation. Glycated hemoglobin (HbA1C) was 8.2% (normal, 4–6%), fasting plasma glucose was 7.25 mmol/l (normal, 3.9–6.1 mmol/l).

In the absence of any mechanical obstruction in the common bile duct or other obvious causes of hepatic injury, and because of the temporal relationship between initiation of methimazole and onset of cholestasis, a diagnosis of drug-induced liver disease was suspected. Treatment with the methimazole was stopped. Propranolol therapy was resumed for symptomatic relief accordingly. Insulin therapy was given to control the blood glucose concentrations starting as short-acting regular insulin 4 U, 4 U, 4 U before each meal and basal acting insulin glargine 10 U. Insulin doses were adjusted according to self-monitoring blood glucose (SMBG) levels (Table 1). During hospitalization, oral UDCA was started 2 days after the patient's admission.

Table 1 SMBG level (mmol/l)

Date	7:00	9:00	12:00	14:00	17:00	20:00	22:00
03/06/09	/	/	/	17.9	6.8	9.0	17.4
03/07/09	12.3	19.6	18.5	9.6	18.2	/	14.5
03/08/09	10.3	13.8	14.2	15.7	10.7	12.8	13.5
03/11/09	6.8	/	/	13.1	12.5	8.4	10.8
03/13/09	5.6	6.6	7.9	6.6	11.3	8.4	8.3
03/19/09	11.8	11.1	11.9	6.2	9.4	3.5	6.8
03/20/09	11.6	11.0	10.1	9.7	11.4	11.1	11.7
03/22/09	10.1	7.6	6.8	8.2	6.1	4.9	5.8

Table 2 Liver function tests

Date	ALT	AST	ALP	γ-GTT	TB	CB
03/06/09	92.5	48.5	301.4	532.6	255.2	206.4
03/13/09	41.7	34.6	204.9	254.1	261.5	223.0
03/18/09	32.0	36.2	197.9	155.2	298.7	254.2
03/26/09	42.9	41.0	182.9	120.9	295.4	250.9
04/07/09	103.2	80.5	199.5	156.8	197.9	172.8
04/22/09	76.8	46.0	267.6	257.3	77.4	68.5
05/07/09	28.9	26.5	243.1	194.0	37.9	32.3
05/19/09	33.3	31.5	247.4	131.6	27.7	15.3

ALT alanine aminotransferase, normal range 0–45 U/l; *AST* aspartate aminotransferase, normal range 0–45 U/l; *ALP* alkaline phosphatase, normal range 40–150 U/l; *γ-GT* gamma-glutamyltranspeptidase, normal range 0–50 IU/l; *TB* total bilirubin, normal range 6–22 μmol/l; *CB* conjugated bilirubin, normal range 0–6 μmol/l

However, after 14 days of UDCA therapy, the patient still had progressive worsening of nausea, anorexia, itching, and jaundice (total bilimbin 298.7 μmol/l, conjugated bilirubin 254.2 μmol/l). Since no improvement was obtained from UDCA therapy, oral treatment with prednisone 0.5 mg/kg/day was added. After 20 days of prednisone therapy, bilirubin values fell significantly (total bilirubin 197.9 μmol/l, conjugated bilirubin 172.8 μmol/l). And within 6 weeks, itching and jaundice completely disappeared. Prednisone therapy was slowly tapered by 5 mg/week after 2 weeks, and discontinued 8 weeks later. Insulin doses were reduced appropriately concurrently. The evolution of serum conjugated bilirubin and ALT levels during UDCA and prednisone therapy was shown in the Table 2. Symptoms and signs had almost completely resolved by the time of the patient's discharge. Serum levels of liver enzymes (ALT and AST) and bilirubin were normal at 12 and 14 weeks, respectively, after the discontinuance of methimazole therapy. For further treatment of hyperthyroidism, the patient would be considered to receive radioactive iodine ablation of the thyroid gland.

Discussion

Adverse reactions to antithyroid drugs occur in less than 10% of patients being treated for hyperthyroidism. Methimazole-induced cholestasis is extremely rare; fewer than 20 cases were reported in the literature [2–4]. In the present case, cholestatic jaundice was most likely caused by methimazole for the following reasons. First, there was a clear temporal relationship between the initiation of methimazole and the development of jaundice 1 month later and the patient's clinical status and laboratory findings were improving with appropriate treatment since admission. Second, the patient appears to have no past history and no recent risk factors for liver disease. And the concomitant liver diseases were excluded to a large extent by proper serologic tests. Third, it is unlikely that the severe cholestasis in our case was related to hyperthyroidism per se. The patient did, in fact, have evidence of hyperthyroidism, with suppression of serum TSH and elevation of free T4 level. But laboratory studies initially obtained from her primary care physician demonstrated that before antithyroid drug treatment, serum bilirubin, AST, ALT, and alkaline phosphatase levels were all normal. Sometimes hyperthyroidism per se can cause elevated serum levels of hepatic enzymes and bilirubin, mostly improved with treatment of hyperthyroidism in all adult cases [5–7]. In our patient, thyroid hormone values had already returned to near normal range, while plasma bilirubin levels were extremely elevated. The thyrotropin level was still suppressed, since it lagged behind the normalization of thyroid hormones by 4–6 weeks. Finally, cholestasis was unlikely to be attributed to propranolol because jaundice resolved despite continued use. Liver biopsy was not performed serially in our case because of the great risks of bleeding and fear as well as discomfort in this old patient.

No specific treatment for drug-induced liver injury exists. Early recognition and drug withdrawal are the keys to management of drug-induced hepatotoxicity. Some studies have reported that UDCA arrested drug-induced cholestasis in two-thirds of cases [8]. In our patient, she experienced a progressive worsening in cholestasis in using this drug during the following 2 weeks. Treatment of prednisone was then attempted after 14 day course of UDCA therapy. This therapy was promptly followed by improvement in clinical and laboratory test results. After 2 months of prednisone treatment, the patient became symptom-free with normal bilirubin levels. Of course, we could not totally neglect the effects of UDCA in the treatment of this case. Combination steroid-UDCA therapy could be of benefit to treat severe and progressive drug-induced cholestasis.

The role of steroids in the management of drug-related cholestatic hepatitis in adults successfully has been reported [9, 10]. But all cases had no history of diabetes that described the use of steroids therapy. And, little has been published on how tight blood glucose control may be maintained when high dose steroid therapy management has to be commenced. Glucocorticoids oppose insulin action and stimulate gluconeogenesis. Steroid dose increments can lead to progressive increase in blood glucose. The hyperglycemia carries an increased risk of infection, especially in hyperthyroid patient with other risk factors such as granulocytopenia. Our patient had 10-year history of type 2 diabetes. Her HbA1c was 8.2%. So insulin therapy was considered firstly. Before starting steroids, normal blood glucose was achieved. After steroid treatment, the blood glucose concentrations were elevated and worsening. Insulin dose was modified according to SMBG. During steroids tapering regiment, there were anticipatory reductions of the insulin dose to avoid a risk of hypoglycemia. SMBG levels were obtained in the range 5.0–8.0 mmol/l. The meticulous control of diabetes was maintained. From our case, individualization of therapy is especially important as the patient began to approach the good control. Because of the need to adjust daily insulin requirement during the steroid therapy was sometimes unpredictable, SMBG was advised. In conclusion, glucocorticoids should be an appropriate therapy for some cases with drug-induced cholestatic jaundice and should not be looked upon as a contradiction in diabetic patients.

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