Langenbecks Arch Chir (1996) 381: 225–227

ORIGINAL ARTICLE

G. P. Schwab · G. J. Wetscher · W. Vogl · E. Redmond

Methimazole-induced cholestatic liver injury, mimicking sclerosing cholangitis

Received: 18 April 1996

Cholestase vom Typ der primär sklerosierenden Cholangitis als Nebenwirkung einer Hyperthyreosetherapie mit Methimazol

Abstract Cholestatic jaundice caused by imidazole derivates is a rare complication of antithyroid therapy. Only 20 such cases have been reported in the literature since the introduction of methimazole in 1949 and of carbimazole in 1953. We present a further case of methimazole-induced cholestatic liver injury, mimicking sclerosing cholangitis, where the etiology has been proven by a clear chronological relationship and the lack of other causative factors.

Zusammenfassung Als seltene Nebenwirkung einer Therapie der Hyperthyreose mit Imidazolabkömmlingen wurde das Auftreten einer mechanischen Cholestase beschrieben. 20 derartige Fälle wurden seit der Einführung von Methimazol 1949 und von Carbimazol 1953 publiziert. Wir berichten über den weiteren Fall einer mechanischen Cholestase unter Methimazoltherapie, die mit dem radiologischen Bild einer primär sklerosierenden Cholangitis einherging.

Schlüsselwörter Cholestatischer Ikterus · Imidazol · Hyperthyreose

Introduction

Antithyroid medication with methimazole and carbimazole has rarely been associated with cholestatic jaundice. Since the introduction of methimazole in 1949 [1] and of carbimazole in 1953 [2], a total of 20 cases of cholestatic jaundice have been described, 13 of which were caused by methimazole [3–12] and 7 by carbimazole [13–16].

We present a further case of methimazole-induced liver injury, mimicking sclerosing cholangitis. The relationship between the hepatic damage and the antithyroid therapy was confirmed by the clinical course.

G. P. Schwab (✉) · G. J. Wetscher
2nd Department of Surgery, University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria

W. Vogl
Department of Internal Medicine University of Innsbruck

E. Redmond
Department of Surgery, Creighton University, Nebraska, USA

Case report

History

A 68-year-old patient was treated preoperatively with methimazole (3×20 mg/day) for manifest hyperthyroidism caused by an adenoma of the right lobe of the thyroid gland. His past history was uneventful and he was not an alcoholic. Furthermore, he was not at risk from hepatitis or human immunodeficiency syndrome and had no signs of congestive heart failure.

Liver function tests were within the normal range before antithyroid therapy was started and regular checks at 2-weekly intervals did not reveal any pathological changes at first. An euthyroid condition was established within 1 month. After about 2 months of therapy, the patient complained of pruritus, jaundiced sclerae and skin, and dark urine. To exclude a viral hepatitis or any kind of mechanical cholestatis, a planned thyroidectomy was postponed and the possible causes of jaundice were evaluated.

Laboratory findings

The following pathological laboratory data were verified (Table 1). Two months after onset of the antithyroid therapy the cholestatic parameters rose. Cholinesterase and prothrombin time, markers of the liver synthesis, remained within the normal range; hepatitis A, B and C serological studies were negative, as were tests for antibodies against nuclei, mitochondria and smooth muscle.

Ultrasound findings

Sonographic examination showed a cholecystolithiasis without any signs of acute inflammation, and the bile duct appeared of normal diameter without any evidence of stones.

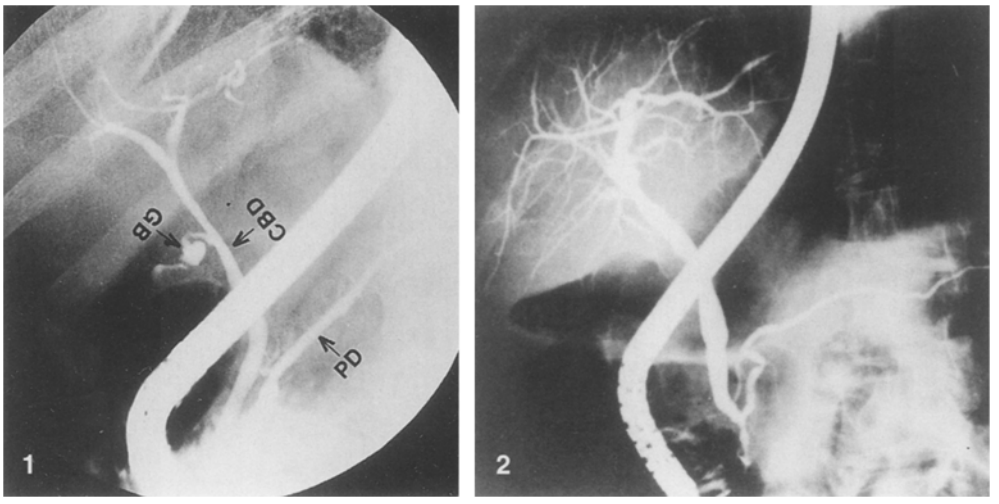

Fig. 1 ERCP finding. Note the marked rarefication of the intrahepatic bile branches (*CBD* common bile duct, *GB* gall bladder, *PD* pancreatic duct)

Fig. 2 Control ERCP 3 months later. Completely unremarkable

Table 1 Laboratory findings at the primary examination (**A**), 8 weeks after onset of antithyroid therapy (**B**), 9 weeks after onset of antithyroid therapy, which is the time of thyroidectomy (**C**), 4 days (**D**), 3 months (**E**) after thyroidectomy

	A	B	C	D	E
T3	15	8.7	8.6	7.3	4.5
T4	52	23.4	21.5	15.7	17.3
TSH	<0.1	0.4	0.4	0.6	2.3
TRH	<0.1	3.0	3.0	3.2	9.0
Total bilirubin	0.5	3.14	12.2	4.5	0.9
Alkaline phosphatase	115	530	752	495	135
Gamma-GT	23	393	478	282	25
SGOT	12	32	63	22	14
SGPT	9	61	78	32	11

Normal ranges:

T3	3.5–9.1 pmol/l
T4	11.8–23.4 pmol/l
TSH (basal)	0.1–4 μU/l
TRH	2.5–20 μU/l
Total bilirubin	0.4–1.0 mg%
Alkaline phosphatase	60–150 U/l
Gamma GT (gamma glutamyl transferase)	12–24 U/l
SGOT (serum glutamic oxaloacetic transaminase)	5–12 U/l
SGPT (serum glutamic pyruvate transaminase)	3–11 U/l

Radiological findings

Since laboratory values clearly indicated cholestatic jaundice, an endoscopic retrograde cholangiopancreatography (ERCP) was performed. This examination showed the extrahepatic ducts to be completely normal while the intrahepatic branches wre strongly rarefied (Fig. 1), as seen in primary sclerosing cholangitis.

The chronological relationship of the cholestatic jaundice to the treatment with methimazole, however, indicated a methimazole-induced pathogenesis. We consequently decided to go ahead with the planned thyroidectomy, while at the same time discontinuing methimazole. Although pathological laboratory values dropped immediately after fininishing the methimazole medication (see Table 1 for results on the 4th postoperative day), complete normalization took almost 3 months. A control ERCP performed after 3 months showed normal intrahepatic ducts (Fig. 2). Further controls over a period of about 1 year revealed no recurrence of the cholestatic jaundice.

Discussion

Antithyroid drugs of the imidazole type are highly effective and commonly used in the treatment of hyperthyroidism. The incidence of side effects is reported to be 1–2% [17]. A very rare complication is the hepatotoxic effect, which is not dose-related and can be ascribed to a "hypersensitivity reaction" [8, 14]. The prompt recurrence of hepatic symptoms after drug rechallenge following a period of withdrawal also points to this [4, 8, 13, 14]. The clinical course of methimazole and carbimazole differs entirely with regard to the hepatotoxic effect, despite the fact that methimazole is a metabolite of carbimazole [17]. While carbimazole has a maximum latent period of 3 weeks, reactions to methimazole become manifest only 1–3 months after exposure [4, 8]. Pathological liver values decrease rapidly when carbimazole is discontinued [4], whereas normalization mostly takes several months with methimazole [8] and may initially even be accompanied by an increased bilirubin level [4].

We considered several differential diagnoses in our patient. Owing to the cholecystolithiasis, revealed by sonography, we suspected choledocholithiasis even though no stones had been found in the ultrasound examination and the diameter of the common bile duct was within the normal range. The absence of pain and the rapid clinical course also caused us to assume the presence of an obstructive tumor. The ERCP examination showed entirely normal extrahepatic bile ducts but a strongly rarefied intrahepatic system. This is a non-specific finding, which may result from imidazole-induced histological changes with periportal edema and granulocytic, partly fibrous infiltrates [4, 8, 14]. Therefore, the diagnosis of sclerosing cholangitis could not be made, because the criteria for this disease, ac-

cording to the literature, were not present in our patient [18]. Virus hepatitis or chronic autoimmune inflammation was unlikely in view of the negative serological data. Liver cirrhosis was a further differential diagnosis that had to be considered from the radiological aspects. Sonography revealed a normal structure of the liver parenchyma and no enlarged portal vein and spleen as signs of portal hypertension. In view of these facts, liver cirrhosis was improbable. Liver injury caused by hyperthyroidism would have disappeared as a result of antithyroid therapy. In addition, an euthyroid condition had been established when jaundice occurred.

Owing to the chronological relationship of the symptoms to drug ingestion, a methimazole-induced pathogenesis was finally assumed. Discontinuation of the drug following thyroidectomy confirmed this assumption. Pathological liver values decreased in a manner typical of methimazole [4, 8]. Complete normalization was achieved only afer 3 months, when ERCP results were unremarkable. Further examinations, such as hepatic punching biopsy, laparoscopy or provocative tests, as recommended in the literature [4, 8, 13, 14], were not indicated from a therapeutic point of view, since the clinical course was unequivocal and testing would have exposed the patient to unnecessary discomfort.

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