Impact of liver inflammation on whole body insulin resistance : a case report on primary biliary cholangitis

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Abstract

Chronic liver diseases such as hepatitis C or non-alcoholic fatty liver disease could be associated with insulin resistance, even in the absence of cirrhosis or significant fibrosis.

In this report, we present the case of a patient who was diagnosed with primary biliary cholangitis and metabolic syndrome. Initial evaluation also revealed diabetes with elevated fasting plasma glucose and glycated hemoglobin. After eight weeks of treatment with ursodeoxycholic acid, a complete normalization of the hepatic biological tests was observed. A few months later, while body weight and abdominal perimeter remained stable, fasting blood glucose and glycated hemoglobin decreased significantly, compatible with diabetes disappearance.

This finding supports the concept that the inflamed liver plays a major role in the pathogenesis of insulin resistance and diabetes occurrence in chronic liver diseases, including primary biliary cholangitis. (Acta gastroenterol. belg., **2019,** 82, **536-538**).

Keywords : primary biliary cholangitis, liver inflammation, diabetes, insulin resistance, macrophages, ursodeoxycholic acid.

Abbreviations : ASAT, Aspartate aminotransferase ; ALAT, Alanine aminotransferase ; GGT, γ-glutamyl transferase ; ALP, Alkaline Phosphatase ; IgM, Immunoglobulin type M ; IgG, Immunoglobulin type G ; IF, Immunofluorescence ; AMA, Antimitochondrial antibodies ; PBC, Primary biliary cholangitis.

A 66-year male Caucasian patient was referred in our hepatology department due to abnormal liver tests detected during a routine checkup (Table 1). Serum alkaline phosphatase levels were observed to be already elevated 10 years ago. The patient had no symptoms and in particular no itching. His past medical history included cholecystectomy, hypertension, hypertriglyceridemia and hypercholesterolemia. He had no familial history of diabetes or chronic liver disease. His treatment included losartan (100 mg/day), aspirin (160 mg/day) and an association of ezetimibe (10 mg/day) plus simvastatin (40 mg/day) in one single tablet, without any recent treatment change. There was no alcohol consumption and he was smoking 6 cigarettes per day.

His physical examination was strictly normal. Body weight was 70.8 kg and height 160 centimeters giving a body mass index of 27.7 compatible with slight overweight. Abdominal perimeter was also enlarged at 98 centimeters.

Initial laboratory findings showed increased transaminases level (ASAT 49 UI/L, ALAT 64 UI/L) together with cholestasis (GGT 481 UI/L, ALP 257 UI/L), without any increase in bilirubin level (Table 1). Serum immunoglobulin levels were as follows : normal IgG level of 1274 mg/dL (normal range : 700-1600) and elevated IgM level at 333 mg/dL (normal range 40-230). Both hepatitis B surface antigen and hepatitis C antibodies were negative. Antibodies against hepatitis B core were positive compatible with past viral infection. Anti-mitochondrial antibodies (AMA) were positive by immunofluorescence (IF) (≥1/40) with a specific M2 subtype. Anti-nuclear antibodies were also positive (1/640). Anti-smooth muscle antibodies were negative. Ferritin level was within the normal range. Elevated fasting plasma blood glucose was also discovered (193 mg/dL). Abdominal ultrasound revealed normal liver.

In this context, a primary biliary cholangitis (PBC) was suspected with the possibility of an overlap syndrome.

A transcutaneous liver biopsy was performed. The liver fragment contained 10 liver acini. The parenchymal architecture was preserved. Most portal tracts were filled with an important inflammatory infiltrate with a nodular aspect (Figure 1A). Many cells within the inflammatory infiltrates were positive for CD68 (a marker of macrophages) with an enlarged appearance (Figure 1B). There was a canalicular proliferation as well as destruction of biliary ducts, as shown by keratin 7 staining (Figure 1C). Some lipid vacuoles were also observed and a low fibrosis level was present at Masson trichrome staining (not shown). Altogether, those results are compatible with PBC without significant fibrosis, discrete steatosis and no argument for auto-immune hepatitis (overlap syndrome) or non-alcoholic steatohepatitis.

Following the confirmation of PBC at liver biopsy, a treatment with ursodeoxycholic acid was prescribed (15 mg/kg/day). No treatment was prescribed for diabetes but an appointment in the endocrinology unit was proposed. Eight weeks after treatment initiation, liver enzymes and IgM levels were assessed, showing significant

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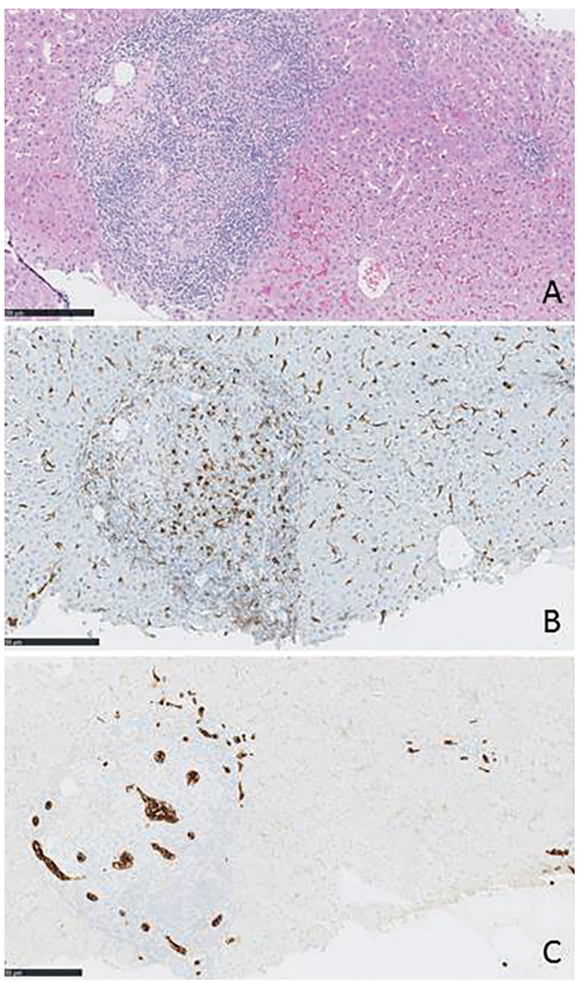
Table — **Patient's biochemical results and body weight evolution from baseline to week 48 of follow-up after treatment initiation**

	Normal range	Baseline	Week 8	Week 40	Week 48
Fasted glucose (mg/dL)	*70-100*	193	-	132	113
HbA1c (%)	*4,0-6,0*	8,60	-	-	6,70
CRP (mg/L)	*< 5,0*	7.0	-	5.0	-
IgM (mg/dL)	*40 230*	333	240	147	-
IgG (mg/dL)	*700-1600*	1274	-	-	-
CK (UI/L)	*20-200*	95	-	-	-
LDH (UI/L)	*< 250*	166	-	-	-
ASAT (UI/L)	*19-48*	49	20	21	-
ALAT (UI/L)	*10-40*	64	15	16	-
GGT (UI/L)	*< 60*	481	39	23	-
ALP (UI/L)	*40-130*	257	95	74	-
Bilirubin (mg/dL)	*< 1.2*	0.3	-	-	-
AMA		≥ 1/40	-	-	Negative
ANA		1/640	-	-	-
ANCA		Negative	-	-	-
IgG_4 (mg/dL)	*1,0-104,0*	51	-	-	-
Weight (kg)		71,4	-	-	72,7

HbA1c : glycated hemoglobin, CRP : C-reactive protein, IgM : immunoglobulin type M, IgG : immunoglobulin type G, CK : creatine kinase, LDH : lactate dehydrogenase, ASAT : aspartate aminotransferase, ALAT : alanine aminotransferase, GGT : gamma-glutamyl transferase, ALP : alkaline phosphatase, AMA : antimitochondrial antibodies, ANA : antinuclear antibodies, ANCA : antineutrophil cytoplasmic antibody, IgG_4 : immunoglobulin type M subtype 4.



improvement of blood alterations following treatment initiation (Table 1). Eight months later, despite the absence of consultation in the endocrinology department and the absence of diabetes medication, blood glucose and liver enzymes were controlled showing complete normalization of both liver tests and IgM levels together with an important decrease in blood glucose level (Table 1). In these conditions, a simple follow-up of blood glucose level was proposed. After 48 weeks of treatment, diabetes had disappeared (blood glucose < 126 mg/dL) together with a marked decrease in glycated hemoglobin and the disappearance of AMA by IF, while the patient's body weight and abdominal perimeter remained stable (Table 1).

Discussion

Primary biliary cholangitis is a chronic liver disease of unknown etiology characterized by progressive intrahepatic cholestasis due to an inflammatory destruction of small intrahepatic bile ducts (1). The majority of the cases are now diagnosed before cirrhosis appearance due to abnormal liver tests detection at routine blood check-up. In contrast, in the past, typical case presentation was a middle-aged woman with pruritus, fatigue, hyperpigmentation and eventually jaundice. Some other

Figure 1. — Liver biopsy showing an important inflammatory infiltrate within the portal tract (hemato-xylin and eosin staining) (A), containing many CD68 positive enlarged macrophages (B), biliary damage and canalicular proliferation evidenced by keratin 7 staining (C).

characteristics such as cholestasis consequences (inducing osteoporosis or hypercholesterolemia) and other autoimmune conditions are also possible. Ursodeoxycholic acid, a synthetic bile acid, has been shown to be safe, well tolerated and to delay disease progression (1). While seropositivity for AMA is not specific to the disease, it is highly sensitive (2). Fluctuation of AMA reactivity has been described during PBC disease course or treatment (1), sometimes with complete conversion of AMA from positive to negative mainly with the IF detection method (2,3). However, it does not seem to correlate with clinical outcomes or with a therapeutic response (4).

Insulin resistance, the first step of diabetes, is defined as the inability of insulin to adequately exert its actions such as glucose uptake stimulation mainly in the skeletal muscle and inhibit endogenous glucose production mainly by the liver (5). Insulin resistance is classically described as the consequence of a chronic low grade inflammation in obese patients. The pathophysiology includes the role of inflammatory adipokines produced by the expanded and inflamed adipose tissue of obese patients, and in particular by its infiltration by adipose tissue macrophages (6). Insulin resistance inducing hyperglycemia is also a well-known clinical entity in intensive care units in a context of acute injury and critical illness (7). Finally, specific liver conditions such as hepatitis C or non-alcoholic fatty liver disease are also associated with insulin resistance and diabetes, even in lean subjects (5,8). Collectively, all those data are consistent with a role of inflammation (systemic, from the adipose tissue or from the liver) in insulin resistance pathogenesis.

Here, we describe for the first time the case of a patient supporting the fact that liver inflammation due to active cholangitis can induce insulin resistance and that an appropriate treatment of the liver condition is able to significantly ameliorate insulin sensitivity and in this case to reverse diabetes. Interestingly, while insulin resistance is also suggested as a possible complication of cirrhosis and/or portal hypertension (9), insulin resistance develops in our case in the absence of significant fibrosis. Important macrophage recruitment is observed in PBC (10,11) mainly in the early stages of the disease (12). This massive macrophage activation was confirmed in our case within portal inflammatory infiltration. In animal models, liver macrophage activation was shown to be an important contributor of hepatic insulin resistance, due to the production of inflammatory mediators altering the insulin signaling cascade (13,14). The data shown here are thus compatible with the role of liver inflammation and not liver fibrosis on glucose homeostasis dysregulation. Importantly, patient's body weight remained stable during follow-up and even mildly increased (a phenomenon already described during ursodeoxycholic acid treatment (15)) leading to the absence of a confounding factor in diabetes disappearance. Unfortunately, insulin levels were not evaluated in this case report. So, we are not able to calculate the Homeostasis Model Assessment for insulin resistance (HOMA-IR).

As a practical point of view, blood glucose level could be measured at the time of PBC diagnosis in order to detect diabetes coexistence. However, some patience could be advised before starting specific glucose lowering agents to see whether specific PBC treatment will ameliorate insulin resistance or not.

Conflict of interest

The authors declare no conflict of interest regarding this manuscript. There is also no financial support.

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