CASE REPORT

Diagnostic value of anti-gp210 antibodies in primary biliary cirrhosis: a case-based review

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SUMMARY

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterised by chronic cholestasis usually associated with antimitochondrial antibodies. Moreover, several types of antinuclear antibodies have been associated with primary biliary cirrhosis. We describe an 83-year-old man, in whom the exploration of a chronic cholestasis led to the diagnosis of primary biliary cirrhosis despite negative antimitochondrial antibodies, regarding the presence of anti-gp210 antibodies. Found in 25% of patients, these antinuclear antibodies must be sought before a strong suspicion of primary biliary cirrhosis with antimitochondrial antibodies negative, as they are highly specific of the disease. They are generally associated with a more aggressive form of PBC.

BACKGROUND

Primary biliary cirrhosis (PBC) is a chronic progressive inflammatory liver disease the diagnosis of which is usually made on the presence of antimitochondrial antibodies (AMA).¹ We report the observation of a patient with negative AMA in whom the diagnosis of PBC was based on the detection of antinuclear antibodies (ANA) with anti-gp210 specificity. This case report highlights the role of these antibodies in cases of suspected PBC.

CASE PRESENTATION

An 83-year-old Caucasian man was referred to hospital for deterioration of general condition with biological inflammatory syndrome. His medical history was significant for arterial hypertension treated with amlodipine, dyslipidemia for which he took rosuvastatin and atorvastatin, and type 2 diabetes controlled by insulin and metformin. His diabetes was complicated by nephropathy with microalbuminuria but without renal failure, and moderate chronic ischaemic heart failure handled with aspirin, furosemide, hydrochlorothiazide and atenolol. His treatment also comprised enalapril against hypertension, heart and renal failures. He denied any exposure to toxic substances, especially alcohol.

Physical examination failed to disclose any abnormality. Laboratory tests revealed a C reactive protein (CRP) level at 204 mg/L, an anicteric cholestasis with γ glutamyltransferase (GGT) at 400 IU/L (8N) and alkaline phosphatase (ALP) at 385 IU/L (3.5N), associated with a normal level of bilirubin, and no hepatic cytolysis. Chest X-ray disclosed a left basal pneumonia, for which a regimen of amoxicillin and clarithromycin was started. Under this treatment, his cholestasis was impaired, with an increase in GGT to 16N. He also

developed a moderate cytolysis, with aspartate aminotransferase at 90 IU/L (2N) and alanine transaminase at 83 IU/L (2N). Abdominal ultrasound was normal. MRI of the biliary tract failed to disclose any abnormality. Serology for viral hepatitis B and C were negative. Ferritin level and transferrin saturation were normal, at 226 mg/L and 13%, respectively. Copper plasmatic level was normal (1.1 mg/L). The ANA titre was at 1 600 with nuclear rim fluorescence pattern. Antiendoplasmic reticulum antibodies and AMA were negative. The hypothesis of hepatic toxicity of antibiotics was finally retained, as far as the liver function disturbances had improved after the antimicrobials disruption. By the way, the hepatic biological tests had only returned to their base level, without normalising.

One year later, the patient was admitted in our internal medicine unit because of persisting cholestasis. He was in good general condition, without fever. He reported occasional right temporal headache associated with temporomandibular joint pain without intermittent claudication or other articular complaint, notably without indications of rhizomelic pseudopolyarthralgia. Clinical examination only disclosed a systolic aortic cardiac murmur and a left femoral arterial murmur. Temporal pulses were present. Laboratory tests revealed a moderate inflammatory syndrome with CRP and fibrinogen levels at 11 mg/L and 6.2 g/L, respectively. Anicteric cholestasis persisted with GGT at 10N (646 IU/L) and ALP at 2.5N (341 IU/L), without cytolysis. The prothrombin time was at 100%. There was a polyclonal hypergammaglobulinaemia at 17.2 g/L (normal value in our laboratory: 8–13.5 g/L) with IgG at 14.3 g/L (N 6.88–12.78 g/L), IgA at 3.52 g/L (N 1.08–3.44 g/L) and IgM at 6.47 g/L (N 0.52–1.46 g/L). Immunological tests confirmed the presence of ANA with a titre of 800, still against the nuclear membrane. Their specificity was found to be anti-gp210 and antipromyelocytic leukaemia protein (anti-PML). Antiliver pancreas antigens, soluble liver antigens (anti-LP/SLA) antibodies were also weakly positive. Other immunological markers were negative, including detection of antibodies against mitochondria, endomysium, actin and LC (liver cytosol), dsDNA, extractable nuclear antigens and antineutrophil cytoplasmic antibodies. The exploration of complement (C3, C4 and CH50) was normal. A temporal artery biopsy disclosed a fibrous endarteritis, with no evidence for giant cell arteritis.

DIFFERENTIAL DIAGNOSIS

The hypothesis of chronic toxic hepatitis is unlikely, as the patient denied any alcohol consumption and as his long-term treatment did not

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include major hepatotoxic molecules. The accountability of antimicrobials is also unlikely: (1) hepatic toxicity of amoxicillin (without clavulanic acid) and azithromycin are poorly reported; (2) hepatic abnormalities are usually reversible at treatment disruption and (3) in our patient, hepatic dysfunction pre-existed to antimicrobial prescription. However, a drug-induced liver injury cannot be fully excluded, because the patient received several drugs and there is no data available in literature about the potential role of anti-gp210 antibodies in drug-induced conditions. Normal abdominal imaging studies ruled out the presence of a biliary tract chronic obstruction. Dyslipidaemia and diabetes were considered as controlled and abdominal MRI did not find any evidence for non-alcoholic chronic hepatitis. Serological tests for chronic hepatic viral infections were negative. Metabolic aetiologies were improbable: ferritin and transferrin saturation coefficient were low as well as copper plasmatic level, eliminating haemochromatosis and Wilson disease, respectively. Other autoimmune hepatic damages were less probable since other immunological markers were negative, and especially for autoimmune hepatitis and sclerosing cholangitis. Giant cell arteritis, which can rarely be associated with chronic cholestasis, can be excluded as far as the temporal artery biopsy histological examination did not disclose any evidence for vasculitis, and as clinical symptoms of Horton disease and rhizomelic arthritis quickly disappeared without corticosteroid therapy.

OUTCOME AND FOLLOW-UP

Given all these considerations, the diagnosis of PBC was retained. Treatment with ursodeoxycholic acid (UDCA) was started in combination with biological monitoring. At 2-year follow-up, the patient was well and hepatic parameters were stable.

DISCUSSION

PBC¹ is a chronic liver disease characterised by inflammatory destruction of small interlobular bile ducts leading to intralobular cirrhosis. It mainly affects women in the fifth decade and represents 2% of cases of death from cirrhosis, with a varying incidence and prevalence according to geographic areas with a possible north-south gradient. Diagnosis of PBC is conventionally based on a combination of clinical, biochemical, immunological and eventually histological evidences. The association of a cholestasis persistently for more than 6 months and elevated levels of AMA allows affirming the diagnosis in the absence of an alternative explanation.² Clinical symptoms of chronic cholestatic liver disease are usual, with a high frequency of itching and sometimes debilitating asthenia that affects 70% and 85% of people, respectively.³⁻⁴ Extrahepatic signs as arthralgia or Raynaud's syndrome are frequent. They can be isolated or included in other immunological diseases associated with PBC such as scleroderma,⁵ Sjogren syndrome⁶ or celiac disease.⁷ By the way, as in our patient, more than 50% of diagnosis of PBC is made in asymptomatic patients, referred to a specialised unit for a chronic elevation of cholestasis markers.¹ Usual biochemical tests disclose a chronic cholestasis lasting more than 6 months. Non-specific biological signs of chronic autoimmune disease can be found, such as haemolytic anaemia or autoimmune thrombocytopenia. Another usual indirect evidence for PBC diagnosis is an increased serum cholesterol level. Histologically, PBC is characterised by a granulomatous destructive cholangitis of interlobular and septal biliary ducts, associated to portal tract infiltration with B cells, CD4 and CD8 T cells, natural killer cells, macrophages and eosinophils.¹ However, the liver biopsy is not recommended for the diagnosis of PBC if biological markers (cholestasis >6 months) and specific immunoassays are positive.² By the way, liver histological analysis

allows assessing the severity of the disease by the importance of bile ducts destruction, inflammation and fibrosis, according to the Ludwig⁷ or Scheuer⁸ scores.

Concerning serology findings, PBC is usually characterised by the presence of AMA, which are generally positive several years before the phase of clinical and biological expression, with a high positive predictive value for the development of PBC. These antibodies have a sensitivity of 90–95% and a specificity of 95–100%.¹⁻⁹ Moreover, almost all patients, including those with negative AMA, present a non-specific elevation of serum IgM.¹ ANA are detectable in 50% of patients with PBC, with two patterns of nuclear fluorescence usually described. First, perinuclear or rim-like immunofluorescence pattern corresponds to ANA recognising proteins of the nuclear envelope such as anti-gp210, antilamin B receptor (1–9% of patients, high specificity) or anti-p62 (13–19% of patients, high specificity) antibodies.²⁻¹⁰ Then, grain or multiple nuclear dots immunofluorescence pattern includes anti-SP100 (20–30% of patients, high specificity) and anti-PML (promyelocytic leukaemia antigen, approximately 20% of patients) antibodies.¹¹

The presence of ANA with rim-like staining immunofluorescence pattern in patients with PBC was first described in 1985 by Ruffati *et al.*¹² Five years later, Courvalin *et al.*¹³ attributed this particularity to antibodies against the gp210 glycoprotein, which constitutes the inner pore of the nuclear membrane. Since then, several studies have shown that anti-gp210 antibodies are detected in approximately 25% of patients with PBC (9–41%) and are therefore not very sensitive. By the way, their specificity is excellent, close to 100%, as they are present only from 0% to 0.4% of controls from different studies (healthy subjects and/or suffering from other autoimmune diseases in particular liver; table 1).¹⁰

Prevalence of anti-gp210 antibodies detection seems to be higher in the 5% of patients negative for AAM, as suggested by the series of Bandin *et al* showing that 46.7% of patients positive for anti-gp210 antibodies in the absence of AMA versus 24.4% in positive AMA patients among 285 patients with PBC.¹⁴ The research of ANA specific for PBC, in particular anti-gp210 antibodies, is now currently recommended in patients with high suspicion of PBC but negative AMA.²

It is not known whether the presence of these antibodies is predictive or not for a particular clinical and biological profile of PBC. Indeed, if it appears in some studies that patients with positive anti-gp210 antibodies had fewer extrahepatic signs (Raynaud's phenomenon, arthralgia),¹⁵ other data are contradictory. Similarly, it is not clear if the presence of these antibodies affects the biological profile of PBC, with the exception of serum IgM level that seems to be lower in anti-gp210 antibodies positive patients.¹⁶

Beyond their diagnostic value, anti-gp210 antibodies are an important prognostic factor in PBC as associated with faster progression to hepatocellular insufficiency and higher mortality. Indeed, comparing mortality caused by liver failure in 25 patients with anti-gp210 antibodies to 88 patients with negative anti-gp210 antibodies, Itoh *et al*¹⁷ found a higher mortality rate in the anti-gp210 antibodies positive patients, with an OR of 3.5 ($p < 0.01$). In an Italian study, Wesierska-Gadek *et al*¹¹ confirmed this data, showing a significantly faster progression of the disease in patients positive for ANA with a circled perinuclear fluorescence pattern. In addition, monitoring anti-gp210 antibodies titre under UDCA could be significant, as suggested by Nakamura *et al*¹⁸ who underlines that the progression to hepatocellular failure is lower in patients with a decrease in titre of anti-gp210 antibodies under UDCA.

Table 1 Summary of the studies evaluating anti-gp210 antibodies in the diagnosis of primary biliary cirrhosis

References	PBC (n)	Control		AMA n (% PBC)	Anti-gp210 antibodies		Se	Sp	Anti-gp210 +and AMA
		n	Description		Technique	n (%PBC)			
Gao <i>et al</i> ²⁰	140	47	Healthy subjects		IB	43/140 (30.5%)	30.5%	100%	
Bauer and Habiort ²¹	117	222	Healthy subjects, other chronic hepatopathy or inflammatory diseases		ELISA	52 (44.4%)	44.4%	99%	
Wesierska-Gadek ¹¹	127	0			IB c-gp210	29/127 (22.8%)			
Nakamura <i>et al</i> ¹⁸	71	192	Healthy subjects, other chronic hepatopathy or inflammatory diseases		ELISA, IB	23/71 (32.4%)	32.4%	100%	
Muratori <i>et al</i> ²²	96	75	Other chronic hepatopathy or inflammatory diseases	83 (86.5%)	ELISA	15/96 (16%)	16%	98.7%	2/13 (15%)
Miyachi <i>et al</i> ²³	175	120			IB c-gp210	46/175 (26.3%)	26.3%	100%	
Bandin <i>et al</i> ¹⁴	285	497	Healthy subjects, other chronic hepatopathy or inflammatory diseases	270 (91.5%)	ELISA	73/285 (25.6%)	25.6%	99.7%	7/15 (47%)
					IB			99.4%	
					IF			96.6%	
Itoh <i>et al</i> ¹⁷	113	162		108 (95.6%)	IB c-gp210	25/113 (22.1%)	22.1%	100%	1/5 (20%)
Luetting <i>et al</i> ¹⁹	42	0			IB	15/42 (35.7%)			
Mattalia <i>et al</i> ²⁴	35	0			IB	9/35 (25.7%)			
Wesierska-Gadek <i>et al</i> ²⁵	43	0			IB c-gp210	12/43 (27.9%)			
Nickowitz <i>et al</i> ¹⁶	159	46			IB r-gp210	15/159 (9.4%)	9.4%	100%	
Lassoued <i>et al</i> ²⁶	150	0			IB c-gp210	40/150 (26.7%)			
Lozano <i>et al</i> ²⁷	38	277			IB c-gp210	16/38 (41.2%)	41.2%	100%	
Ruffati <i>et al</i> ¹²	63				Rim-like ANA	18/63(28.6%)			

ANA, antinuclear antibodies; AMA, anti-mitochondrial antibodies; c/r-gp210, cellular/recombinant gp210; IB, immunoblot; IF, immunofluorescence; PBC, primary biliary cirrhosis; Se, sensibility; Sp, specificity.

The pathogenic role of these antibodies remains unknown. For example, they are usually still detectable in serum of patients who had undergone a liver transplantation, but without any sign of PBC activity in graft biopsies.¹⁹ However, Nakamura *et al*¹⁸ showed an increased expression of gp210 antigen in epithelial cells of patients with PBC and that its expression level was positively correlated with histological activity of the disease, suggesting a pathogenic role of antigen gp210 itself.

In conclusion, this case report highlight the role of anti-gp210 antibodies, representing a class of highly specific ANA detected in patients with PBC. Their advantage lies partly in the AMA-negative PBC diagnosis, and second as a predictive factor of poor prognosis.

Learning points

- ▶ Anti-gp210 antibodies represent an unrecognised but highly specific class of antinuclear antibodies detected in patients with primary biliary cirrhosis (PBC).
- ▶ Their advantage lies partly in their ability to diagnose PBC in case of negativity of antimitochondrial antibodies.
- ▶ They constitute a predictive factor of poor prognosis.

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