International Journal of
Autoimmune Disorders & Therapy
Mini Review Open Access

Significance of Antinuclear Antibodies in Primary Biliary Cirrhosis

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Abstract

Primary Biliary Cirrhosis is an autoimmune liver disease characterized under serological profile by anti mitochondrial antibodies. In the last years many studies on the frequency and significance of Antinuclear antibodies have been performed. In this quick review we will focus our attention on the antinuclear reactivities specific for PBC.

Publication History:
Received: December 08, 2014
Accepted: May 14, 2015
Published: May 16, 2015

Introduction

Primary Biliary Cirrhosis is a chronic autoimmune liver disease slowly progressive to the end stage liver disease. As all the diseases with an autoimmune pathogenesis it affects predominantly female gender (ratio 9:1) [1]. The main parameters to reach for a diagnosis in the clinical setting are represented by intrahepatic chronic cholestasis, seropositivity for antimithocondrial antibodies – AMA - and liver histology with biliary damage [2].

At least two of these three paramenters have to be satisfied to perform a PBC diagnosis. AMA have a high disease sensibility and specificity but some patients (5-10%) lack this autoreactivity [3].

In the last years several studies on the frequency and significance of autoantibodies other than AMA in PBC have been performed, in particular on anti-nuclear antibodies (ANA); in this short review we'll focus our attention on the ANA reactivities specific for PBC (Table 1).

Reactivity	Method	Antigen source	Approach
Multiple nuclear dots	Immunofluorescence	Hep2 cells	Immunomorphological
Anti Sp100	ELISA/Immunoblot	Recombinant protein	Immunochemical
Anti PML	ELISA/Immunoblot	Recombinant protein/purified protein	Immunochemical
Rim-like/Membranous	Immunofluorescence	Hep2 cells/Rat tissue	Immunomorphological
Anti-gp210	ELISA/Immunoblot	Recombinant protein	Immunochemical
Anti-p62	ELISA/Immunoblot	Recompbiant protein/purified protein	Immunochemical
Anti-LBR	ELISA	purified protein	Immunochemical

Table 1: Antinuclear PBC specific.

MND/Anti-Sp100/anti-PML

The multiple nuclear dots – MND - (figure 1) is an immunomorphological pattern and it can be observed on Hep2 cells where the positivity of 5-15 nuclear bodies and the absence of positivity of mithosis phase make it different from the anticentromere antibodies where the mitosis are positive (figure 1 and figure 2) [4]. The autoantigens implicated in MND pattern are represented by Sp100 and promyelocytic leukemia –PML- (both Nuclear Bodies proteins); Sp100 is so called because its electrophoretic mobility is around 100 Kd, even if its true molecular weight is of 53 kD; it seems have a regulatory role in the physiological cellular setting and its expression is greatly conditioned by several events such as stress, heat and viruses; the dominant autoepitope is localized on its carboxy terminal region [5,6].

PML is an other NB protein that co localizes with Sp100 and shows a similar behaviour during infection, stress and heat shock; similarly to Sp100 also PML seems to have a regulatory funcion in several cellular metabolic processes [5].

In the last years many studies from many countries have been performed on the sensibility and specificity of anti MND/antiSp100/ anti PML, and on their clinical significance.

The frequency of detection of MND/anti-Sp100 varies from 9% to 42% in the different studies, and the specificity were from 64% to 100% [3,7-13]; there are studies where the positivity of MND/ antiSp100 was not strictly related to PBC; for example Wichmann [14]found that only 34% of their MND/antiSp100 positive patients had PBC, while the remainig patients had other hepatic diseases or reumatological disorders; similarly Pawlotsky et al. [15] found that 33% of their MND positive patients were affected by immunological disorders but not by PBC. In our experience it is only partially true, since we found some cases of reumatological patients MND positive but anti-Sp100 negative, but all our patients MND positive/anti-Sp100 positive were affected by PBC, showing a very high specificity of antiSp100 antibodies [3]. The different specificity between MND and anti Sp100 is probably caused by a different method in the search for the MND (indirect immunofluorescence) and antiSp100 (ELISA), different selection criteria of the patients and different genetic background of the populations studied. Indeed it is also important in immunofluorescence practice the choice of secondary antibody since it has been shown as the use of IgG isotypes as secondary serum determines a higher frequency of detection of MND pattern [16].

In a recent metanalysis on the sensitivity and specificity of anti-Sp100 in PBC there were only few studies where the specificity was less than

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Citation: Muratori P, Muratori L (2015) Significance of Antinuclear Antibodies in Primary Biliary Cirrhosis. Int J Autoimmune Disord Ther 1: 105. doi: http://dx.doi.org/10.15344/ijadt/2015/105

90% and all these studies presented low number of patients [9,12,13].

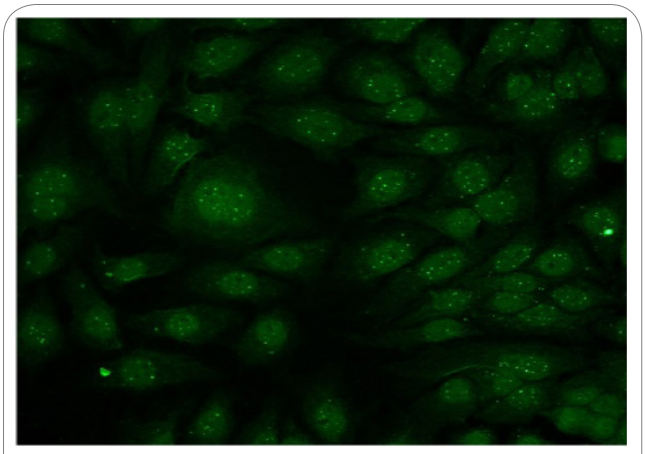

Figure 1: MND pattern (20 x) on HEp-2 cells characterize by the positività of 5-15 dots per nuclei and negativitá of mithosis.

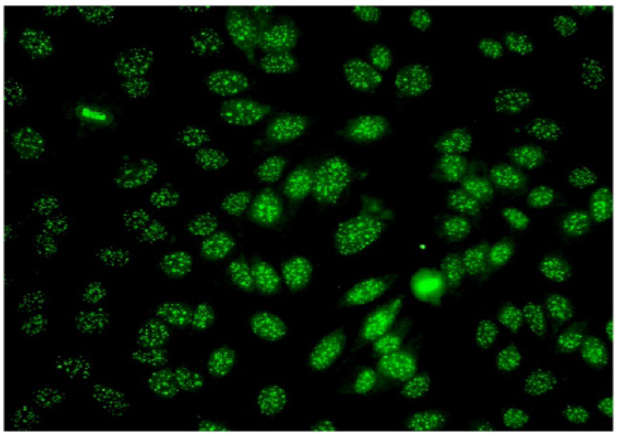

Figure 2: anti centromere pattern characterized by a positività of mithosis and a major number of positive dots

The high degree of specificity of anti-Sp100 antibodies gives them a potential diagnostic role when AMA is absent, while they don't seem to have a clinical or prognostic significance [11].

With respect to anti-Sp100 antibodies, the anti-PML reactivity is less studied and the few data available show a prevalence in PBC patients similar to that of anti-Sp100 [9,17].

Rim-Like/Membranous Pattern/Antinuclear Pore Complex antibodies

The other big family of Antinuclear antibodies specific for PBC is represented by Rim-Like/Membranous pattern. It can be easily detected on the Hep2 giving a positive immunoreaction of the nuclear membrane (Figure 3).

The autoantigens underlying RL/M pattern were identified as components of the nuclear envelope [18]; it consists of three different nuclear structures closely interconnected; nuclear lamina, nuclear pore complexes and nuclear membranes (inner and outer) [19,20]; The more intruiguing component from our point of view is the nuclear pore complex, an anatomical and functional structure located in the nuclear envelope, that allows and regulates the diffusion of proteins between cytoplasm and nucleus [20].

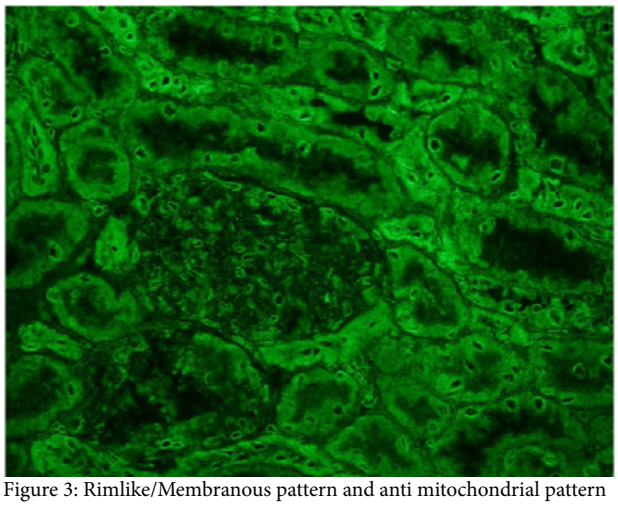

Figure 3: Rimlike/Membranous pattern and anti mitochondrial pattern on kidney rat tissue (20 x).

Over 80 proteins belong to Nuclear Pore Complex and two of them have been shown to have immunogenic properties with PBC sera, and they are named on the basis of their MW, gp210 and p62 18).

An other autoantigen belonging to nuclear membrane is the receptor for the lamina B (LBR) [18] a protein that anchors the nuclear lamina and the heterochromatin to the inner nuclear membrane in interphase.

In the literature there are many studies on the frequency of anti NPC antibodies in PBC [11,16,21-26]; the sensitivity and specificity of the anti NPC antibodies varied as a function of several parameters; number of patients and matched controls, tests used, geographical origin of the populations studied.

When we analyze the presence of antiNPC antibodies by IIF (expressed by RL/M pattern on Hep 2 cells) the frequency of detection ranged from 5% to 53% in the different experiences [11,16,21,22]

Similarly many studies about the frequency and clinical significance of anti-gp210 in PBC performed in the last years presented different degrees of sensitivity (ranging from 6% to 44% in the different experiences), and specificity (62% to 100%) [27]; It's right to point out that studies expressing low specificity of anti gp210 are those who have used a small number of controls [12,13]. Given the high specificity of the test, under the diagnostic profile the significance of anti-gp210 is more attractive when AMA is absent than when it's present; in some studies the presence of anti-gp210 was found to have a strict association with a poor prognosis; in particular in our experience [11] anti-gp210 correlated with a more aggressive and evolutive disease; similar results were described in the experience of Nakamura et al [28], while in Milkiwicz's study [29] a significant higher rate of anti-gp210 positive patients needed an orthotopic liver transplantation or reached the end stage of liver disease than anti-gp210 negative ones.

On the presence of antibodies anti-p62 in PBC there are fewer data compared to the anti-gp: however, the frequency of this antibody is highly conditioned by the antigen used and varies from 13% of the cases when rat liver nuclear envelope to more than 50% when immunoprecipitation with purified human p62 is used as antigen source [30]. Unfortunately anti-p62 is not specific for PBC since it can be found also in 13% of patients with Sjiogren syndrome.

Similarly to anti-p62 only few studies report frequency and clinical significance of anti-LBR antibodies in PBC patients. Nickowitz described a frequency of 1% of positivity for anti-LBR in 159 PBC patients [23]; we found a 6% of frequency on 96 patients [11] and Miyachi 9% on 175 patients [26]. The most isteresting result was the absolute absence of positivity for anti-LBR in control populations, giving this serological marker the highest specificity for PBC. Clearly its clinical usefulness is limited by the very low sensitivity.

Competing Interests

The authors have no competing interests to declare.

Author Contributions

All the authors substantially contributed to the study conception and design as well as the acquisition and interpretation of the data and drafting the manuscript.

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