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Prognostic implications of extra-hepatic clinical manifestations, autoimmunity and microscopic nail capillaroscopy in patients with primary biliary cirrhosis☆

Begoña Marí-Alfonso[a,*], María José Amengual-Guedan[b], Mercè Vergara-Gómez[c], Carmen Pilar Simeón-Aznar[d], Vicente Fonollosa-Plà[d], Esther Jove-Buxeda[a], Juan Oliva-Morera[e], Carles Tolosa-Vilella[a]

[a] *Servicio de Medicina Interna, Corporación Sanitaria y Universitaria Parc Tauli, Instituto Universitario Parc Taulí, Sabadell, Barcelona, Spain*
[b] *Servicio de Laboratorio de Inmunología, UDIAT, Corporación Sanitaria y Universitaria Parc Taulí, Instituto Universitario Parc Taulí, Universidad Autónoma de Barcelona (UAB), Sabadell, Barcelona, Spain*
[c] *Servicio de Hepatología, Corporación Sanitaria y Universitaria Parc Taulí, Instituto Universitario Parc Taulí, Universidad Autónoma de Barcelona (UAB), Sabadell, Barcelona, Spain*
[d] *Servicio de Medicina Interna, Hospital Universitario Vall d'Hebrón, Barcelona, Spain*
[e] *Unidad de Estadística, Fundación Parc Taulí, Corporación Sanitaria y Universitaria Parc Taulí, Instituto Universitario Parc Taulí, Universidad Autónoma de Barcelona (UAB), Sabadell, Barcelona, Spain*

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ABSTRACT

Background and objectives: Primary biliary cirrhosis (PBC) is associated to any systemic autoimmune disease (SAD), in particular systemic sclerosis (SSc).

To investigate the prevalence of SAD in a cohort of patients with PBC, specifically the prevalence of SSc and its clinical subtypes, and determining the clinical and biological profile of patients with associated PBC and SSc.

Methods: Observational study of 62 patients with PBC following a protocol that included an anamnesis and physical examination to detect the presence of SAD as well as a nailfold capillaroscopy and an immunological study with specific SSc autoantibodies. A comparative analysis was conducted between patients with isolated PBC and patients with PBC and an associated SAD.

Results: SAD was associated to PBC in 22 patients (35.4%), and SSc was the most frequent illness, identified in 13 cases (21%). Five patients (8%) without previous diagnosis of SAD fulfilled pre-scleroderma criteria, according to LeRoy and Medsger criteria. The presence of anticentromere antibodies (54.5% vs. 5%, $P < 0.001$) was the unique immunological determination identified more frequently in patients with PBC-SAD. The SSc suggestive capillary pattern was visualized in 11 patients (20.4%), mainly the slow pattern. No factors associated with greater morbi-mortality were identified in the PBC-SAD group.

Conclusions: It does exist a subgroup of patients with PBC and clinical–biological features suggestive of an SAD, which advise a protocolized study to detect early the association to an SAD.

Implicación pronóstica de las manifestaciones clínicas extrahepáticas, autoinmunidad y capilaroscopia ungueal microscópica en pacientes con cirrosis biliar primaria

Palabras clave:
Cirrosis biliar primaria
Enfermedad autoinmune sistémica
Autoinmunidad

RESUMEN

Introducción y objetivos: La cirrosis biliar primaria (CBP) se asocia a algunas enfermedades autoinmunes sistémicas (EAS), en particular a la esclerosis sistémica (ES).

Determinar la prevalencia de EAS en una cohorte de pacientes con CBP, específicamente la ES y sus diferentes subtipos clínicos, y establecer el perfil clínico-biológico propio de estos pacientes.

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* Corresponding author.
E-mail address: bmari@tauli.cat (B. Marí-Alfonso).

Capilaroscopia
Esclerodermia

Métodos: Estudio observacional de 62 pacientes con CBP, con un protocolo que incluía una anamnesis y exploración física dirigidas a detectar una EAS, la realización de una capilaroscopia ungueal microscópica y un amplio estudio de autoinmunidad, incluido el perfil de anticuerpos específicos de ES. Se realizó un análisis comparativo entre el grupo de pacientes con CBP aislada y los pacientes con CBP y una EAS asociada.
Resultados: Se asoció una EAS en 22 pacientes (35,4%), y la ES fue la entidad más frecuente (21%), del subtipo cutáneo limitado (11%). Cinco pacientes (8%) sin EAS previa cumplían criterios de preesclerodermia, según los criterios de LeRoy y Medsger. Los anticuerpos anticentrómero (54,5 vs. 5%, $p < 0{,}001$) fueron el único parámetro inmunológico identificado con mayor frecuencia en pacientes con EAS. El patrón capilar sugestivo de ES se visualizó en 11 pacientes (20,4%). No se identificaron factores asociados a mayor morbimortalidad en ningún grupo.
Conclusiones: Existe un subgrupo de pacientes con CBP con características clínico-biológicas que sugieren la asociación con una EAS, con elevada probabilidad, y que recomiendan el estudio protocolizado de estos pacientes con CBP para detectar de forma precoz EAS.

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease characterized by inflammation and destruction of small and medium calibre bile ducts and deposition of fibrotic tissue with a progressive course that can cause liver failure. The aetiology is unknown, but the most accepted is the autoimmune hypothesis since the PBC is often associated with other autoimmune diseases or is accompanied by non-organ specific autoantibodies. Some studies show that systemic sclerosis (SSc) is the systemic autoimmune disease (SAD) most frequently associated with PBC, in particular, the limited cutaneous subtype (3–50% of cases).[1–5] Thus, anti-centromere antibodies (ACA), specific of SSc and/or microvascular anomalies suggestive of SSc can be detected through microscopic nailfold capillaroscopy (capillaroscopy from now on), in 30% and 42% of patients with PBC, respectively. In some studies, their presence has been linked to a higher incidence of symptoms and/or signs suggestive of SAD, Raynaud's phenomenon in particular.[6–10]

Some authors have indicated that PBC and SSc are associated with increased morbidity and mortality compared to the general population. However, at present, it remains a controversial claim.[11,12] Recent prospective studies that compare patients with PBC and SSc and patients with isolated PBC, adjusted for total bilirubin figures, show a similar mortality in both groups. In patients with associated SSc, death causes are related to SSc.[13]

SSc is characterized by the appearance of microvascular damage, excessive accumulation of collagen fibres in the skin and internal organs, and an inappropriate autoimmune response directed against multiple cellular antigens. Currently, the main prognostic factor for SSc is the extension of cutaneous sclerosis,[14] why most disease experts continue to use the classification proposed by LeRoy et al., 1988.[15] In it, there are 2 large groups of patients with SSc, the subtype SSc with limited scleroderma (lSSc), and the SSc subtype with diffuse scleroderma. However, there is a significant number of patients with unobvious SSc clinical manifestations which are diagnosed late. Most of these patients belong to the group with limited SSc, with little or no cutaneous sclerosis,[16] and a group of patients with pre-scleroderma (pre-SSc), defined according to the classification criteria proposed by LeRoy and Medsger of 2001.[17] The latter group with a high probability of developing into established SSc.[18]

The main objective of this study is to determine the prevalence of associated SAD, particularly SSc, in a cohort of patients with PBC. Secondary objectives investigated are whether patients with PBC associated with a SAD have a specific clinical and biological profile when compared to patients with isolated PBC, as well as the possible prognostic factors related to the association of both autoimmune diseases.

Patients and methods

This is an observational study conducted in the Corporación Sanitaria Universitaria Parc Taulí, Sabadell (Barcelona), with a population catchment area of 430,000 inhabitants. During the study period, from January 1990 to December 2011, 94 patients were identified with the diagnosis of PBC, 62 of which met the following inclusion criteria: (1) diagnosis of PBC, according to the criteria of the *American Association of the Study of Liver Diseases*[19,20]; (2) 18 years of age or over; (3) current clinical follow-up by the Hepatology Unit and (4) signed informed consent to participate in the study. 32 patients were excluded for the following reasons: death prior to the start of the study, chronic liver disease of toxic or infectious origin associated with PBC and any reason that would hinder completion of the study protocol, which is detailed in Fig. 1. The project was approved by the Clinical Research Ethics Committee of the Hospital de Sabadell.

The study protocol included a single medical visit in which the history and physical examination aimed at detecting symptoms and signs suggestive of extrahepatic SAD and capillaroscopy was performed. After the inclusion of patients in the study, serum samples from one of the regular blood tests requested by the physicians responsible for the patients at the Hepatology Unit were identified. The serum aliquots obtained were frozen at −80 °C until their biochemical and immunological study.

Definition of clinical manifestations

- *Peripheral vascular manifestations*: presence of Raynaud's phenomenon, with or without digital ulcers or residual scarring ischaemic lesions in fingertips or acroosteolysis.[21]
- *Cutaneous manifestations*: presence of sclerodactyly, telangiectasia and skin calcinosis.
- *Sicca syndrome*: it was assessed when the patients reported ocular or oral dryness spontaneously, with or without ocular signs or hyposecretion in the Schirmer test or salivary scintigraphy, unrelated to the intake of hyposecretion-inducing drugs and considered disproportionate by their doctor.[21]
- *Gastrointestinal disease*: the following diagnoses were considered as gastrointestinal disease associated with SSc: *oesophageal disease*, if hypomotility of the 2 lower thirds of the oesophagus was confirmed by manometry; *gastric disease*, if gastric hypomotility was detected by barium examination or manometry; *intestinal disease*, if intestinal hypomotility is demonstrated by manometry, malabsorption syndrome by breath test or intestinal pseudoobstruction by radiography or computed tomography.[21,22] The presence of gastroesophageal reflux together with consistent symptoms, with or without specific diagnostic tests, was considered.