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Serum BAFF and APRIL levels in patients with PBC

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Abstract B-cell-activating factor belonging to the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) are known to be involved in the occurrence of autoimmune diseases. We assessed serum levels of these cytokines in PBC patients. Serum BAFF levels were significantly higher in PBC patients than in healthy controls (1253.9±741.4 vs. 722.8±199.2 pg/ml; $p<0.0001$) and HCV-infected patients (1253.9±741.4 vs. 871.0±251.1 pg/ml; $p=0.015$). Whereas changes in serum APRIL levels were not significant among these groups, there was a significant correlation between BAFF and AST ($R=0.278$, $p=0.003$) or total bilirubin ($R=0.363$, $p=0.0006$) in PBC patients. Furthermore, serum BAFF levels were elevated in PBC patients with advanced interface hepatitis. Our data indicate that serum levels of BAFF and APRIL are differentially regulated and serum BAFF levels are significantly elevated in PBC patients. These findings suggest that BAFF may serve as a modulator of the clinical and/or serological manifestation in PBC patients.

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease, characterized by biliary epithelial cell damage, leading to liver cirrhosis and liver failure [1]. The presence of lymphoid infiltration in the portal tract of PBC suggests that an autoimmune response is directed against biliary epithelial cells (BEC) [2]. Although the pathogenesis of PBC remains completely unresolved, it is generally accepted that, in addition to the auto-antibodies-producing B cells, T cells are pivotal to disease progression [3–5]. The serologic hallmark of PBC is the presence of auto-antibodies to mitochondria, especially to E2 component of the pyruvate dehydrogenase complex (PDC) [6]. The pathogenic mechanism is believed to caused by a defect in immunological tolerance, resulting in activation of PDC-E2-specific B lymphocyte and the production of auto-antibodies [7]. Recent findings suggest that B cell autoimmunity in PBC is affected by enhanced innate immune response and cytokine–cytokine-receptor interaction [8]. Diverse cytokines are over-expressed in liver and sera of patients with PBC. Previous data suggest a significant role of Th1 cytokines in the pathogenesis of PBC

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Table 1 Clinical data from PBC patients and controls.

Patients	*n*	Age (years)	Gender (male/female)	AST (U/L)	ALT (U/L)	TB (mg/dl)	ALP (U/L)	IgG (mg/dl)	IgM (mg/dl)	ANA positive (%)	AMA positive (%)
PBC	114	59.8±11.4	16/98	60.6±57.3	63.3±64.6	1.2±2.2	624.9±513.6	1902±630	455±390	51/81 (63%)	106/114 (93%)
CHC	28	58.6±11.2	12/16	66.1±49.4	90.3±76.2	0.7±0.2	NT	NT	NT	NT	NT
Healthy controls	50	42.2±13.6	10/40	NT	NT	NT	NT	NT	NT	NT	NT

CHC, type C chronic hepatitis; ANA, anti-nuclear antibody; AMA, anti-mitochondrial antibody; TB, total bilirubin; NT, not tested.

[9]. However, Th2 cytokines, such as IL-5, IL-6 and IL-10, also have been detected in PBC livers [10], indicating that both Th1 and Th2 cytokines might be involved in the pathogenesis of PBC during different stages of PBC.

BAFF is a key factor controlling B cell survival and maturation and its over-expression promotes autoimmunity [11,12]. High levels of BAFF have been found in the sera of patients with autoimmune diseases and BAFF levels correlate with disease activity and/or titers of pathogenic auto-antibodies [13,14]. BAFF is expressed by monocytes, macrophages and dendritic cells and at lower levels by T cells [15]. BAFF over-production disrupts B cell tolerance and leads to autoimmunity [16]. Therefore, excessive BAFF production is likely to exacerbate disease pathogenesis through inappropriate stimulation of B cells [17]. Another member of the TNF ligand superfamily related to BAFF is a proliferation-inducing ligand (APRIL) [18]. The ability of BAFF to promote both autoimmunity and B lymphoma is clear; however, the precise role of APRIL in autoimmune diseases has yet to be fully elucidated.

Our aim was to investigate the role of serum BAFF and APRIL in PBC patients by comparison with other liver diseases and assess its relationship with liver function tests and liver histological findings.

Materials and methods

Patients and serological studies

One hundred fourteen PBC patients and 28 chronic hepatitis C (CHC) patients were enrolled in this study (Table 1). Written informed consent was obtained from each patient, and the study was approved by the institutional Ethics Committee for Human Research. All PBC patients were seronegative for antibodies to hepatitis A, B, C or other hepatotropic viruses. In addition, sera from 50 healthy volunteers were used as controls (Table 1). All serum samples were stored at −20 °C until use. Total gammaglobulin levels were determined by standard serum protein electrophoresis. The antibody titers to mitochondrial antigens MIT3 (recombinant proteins containing PDC-E2, BCOADC-E2, OGDC-E2) were determined using ELISA kits (INOVA Diagnostics, San Diego, CA), and antibody titers more than 25 U/ml were interpreted as positive according to the manufacturer's protocol and instructions.

Liver biopsy specimen and histological examination

Liver biopsy specimens from 48 PBC patients (7 male, 41 female) were histologically analyzed. The histological variables examined included fibrosis (0–4) (0, absent; 1, expansion of fibrosis to parenchyma; 2, portal–central or portal–portal bridging fibrosis; 3, presence of numerous fibrous septa; 4, cirrhosis), portal inflammation (0–3) (0, absent; 1, mild: cell infiltration 2, moderate: dense infiltration of one portal area; 3, severe: dense infiltration of more than 2 portal areas), interface hepatitis (0–3) (0, absent; 1, mild: interface hepatitis less than one third the circumference of one or two portal tracts; 2, moderate: interface hepatitis less than two thirds the circumference of one or two portal tracts; 3, severe: interface hepatitis more than two thirds the circumference of one or two portal tracts), lobular inflammation (0–3) (0, absent; 1, mild; 2,