Editorial

Anti-mitochondrial autoantibodies—milestone or byway to primary biliary cholangitis?

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Anti-mitochondrial autoantibodies (AMA) are a signature autoantibody of primary biliary cholangitis (PBC), formally known as primary biliary cirrhosis (1), and are detected in sera of 95% of patients with PBC, while scarcely found in patients with other disorders including autoimmune diseases (2,3). Based on this high specificity and sensitivity of AMA for diagnosis of PBC, clinical practice guidelines from the US, Europe and Japan strongly agree with the diagnosis criteria of PBC (4-6). Namely, the diagnosis of PBC can be made if a patient meets at least two of three items; chronic elevation of cholestatic enzymes, presence of AMA, and histological findings consistent with PBC. Even in patients in whom AMA are not found in sera with routine method such as indirect immunofluorescence using rat liver, kidney and stomach tissue sections, AMA can be detected with other methods with high sensitivity such as ELISA or immunoblotting using recombinant mitochondrial proteins as antigens (7,8). Thus, detection of AMA is a robust hallmark of PBC, and therefore it is not surprising that researchers are tempted to consider that AMA are not a simple biomarker of PBC but are closely related to etiology of the disease.

AMA are directed against mitochondrial proteins known as 2-oxoacid dehydrogenase complex family, located at the inner membrane, mainly consisting of pyruvate dehydrogenase complex-E2 (PDC-E2), branched chain 2-oxo acid dehydrogenase complex-E2 (BCOADC-E2), and oxoglutarate dehydrogenase-E2 (OGDC-E2) (9,10). Production of AMA clearly indicates tolerance breakdown against these autoantigens at both B cell and T cell level. PDC-E2 specific CD4+ T cells are accumulated in liver of patients with PBC (11). Furthermore, mitochondrial antigen-specific T cells are detected in AMA-negative PBC patients, suggesting that breakdown of tolerance against mitochondrial autoantigens is present irrespective of AMA status (12). On the other hand, mitochondrial autoantigens ubiquitously exist all over the body and are hidden within cell membranes, while it is well recognized that small to medium sized biliary epithelial cells (BECs) are exclusively damaged by autoimmune reactions in PBC. Why are B and T cells specifically targeted to mitochondrial antigens responsible for bile duct injury, not eliciting other tissue damages?

In 2009, Lleo *et al*. provided a key to solve this mystery regarding tissue specificity (13). They found immunologically active PDC-E2 was found to localize unmodified within apoptotic blebs of human intrahepatic BECs, but not within blebs of various other epithelial cell lines. Thus AMA are accessible to the mitochondrial autoantigens within apoptotic blebs, without penetration into the cell. Later, they also demonstrated that contact of AMA with PDC-E2 within apoptotic blebs (apotopes) resulted in markedly intense inflammatory cytokines production with help from macrophages (14). These sophisticated experiments clearly provided a clue to unravel missing link between presence of AMA and etiology of PBC.

Then, a next question would be as follows: do all

individuals who are AMA seropositive subsequently develop PBC? It is known that AMA are occasionally detectable in healthy individuals (15,16), or patients with other autoimmune or non-autoimmune diseases (17,18). If presence of AMA would be necessary and sufficient for eliciting PBC, these healthy individuals or patients with other diseases inevitably develop PBC in the long run. Results from follow-up study for these individuals and patients have been contradictory, possibly due to design of the studies; rather old study, retrospective nature, small population, and performed in restricted area.

In a recent issue of the *Hepatology*, Dahlqvist *et al*. published a large-scale, prospective study to elucidate longitudinal outcomes of AMA-positive individuals, without established diagnosis of PBC (19). In this work the authors conducted a nationwide network of 63 immunology laboratories in all over France, and identified 1,318 positive AMA tests in 1,318 patients during 1 year. They asked the prescribing physicians to send clinical data from these patients and finally obtained 720 patients with an exploitable medical datasets. Among 720 patients, 216 (30%) were patients already diagnosed as having PBC, 275 (38%) were newly diagnosed as PBC, and 229 (32%) were patients without established diagnosis of PBC. Their main attention was paid on these 229 patients, AMA-positive but without PBC, and they further obtained follow-up data from 92 (40%) among 229 patients [follow-up period 4.0 (range, 0.5–7.3) years]. Very interestingly, development of PBC was reported in only 9 (10%) out of 92 patients, and the 5-year incidence rate of developing PBC was 16%. Nevertheless, whereas no patient died from PBC, the 5-year overall survival rate was 75%, significantly worse compared to 90% in an age/gender matched French control ($P<0.05$).

Of course there are several criticisms regarding this study. First, among 229 AMA-positive patients without a diagnosis of PBC, liver biopsy was done in only 28 patients (19%). As mentioned, the diagnosis of PBC requires at least two out of three items; chronic elevation of cholestatic enzymes, AMA positivity, and histological findings. If AMA are detectable in a given patient, yet serum cholestatic liver enzymes are within normal limit, histological findings of the liver are inevitably required to diagnose or exclude PBC. Among 221 patients who were AMA seropositive yet lacking an opportunity to have a histological diagnosis, patients with PBC might be present. Second, this study is a prospective one, yet follow-up rate (40%) was very low. A variety of biases might go mixed—some patients might be consulted to tertiary centers after establishment of PBC diagnosis, or might die due to complications derived from PBC. Third, as the authors appropriately stated, the persistence of AMA in time were not evaluated. In clinical practice, detection with high titers followed by disappearance of AMA are occasionally observed in some patients, especially during clinical course of infectious diseases. It is quite reasonable to assume that some patients who were AMA seropositive at entry became seronegative during follow-up. PBC is a chronic and insidious disease with a long progression time, and therefore observational period in this study (4 years in average) might not be sufficient. The higher mortality of these populations, suggesting a link between presence of AMA and non-hepatic diseases leading to mortality, is another mystery.

Nevertheless, this large-scale prospective study provides us an important information in terms of etiology of PBC. Relatively low rate of developing PBC, 16% at 5-year, clearly indicates that presence of AMA is definitely required, but is not sufficient, for developing PBC. It is true that AMA plays a crucial role in etiology of PBC, yet there appear to be a missing link between AMA and PBC. Prospective, multicenter, large-scale clinical studies, enrolling continuously AMA seropositive patients who are lacking PBC proved by liver biopsy, are necessary to clarify this link. This is also important to solve the question whether presence of AMA is really associated with non-hepatic mortality, raised from the study of Dahlqvist *et al*. in the *Hepatology*.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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