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Editorial

Is anti-pyruvate dehydrogenase complex a predictor of the development of primary biliary cirrhosis?

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The follow-up of asymptomatic persons with antibodies to pyruvate dehydrogenase in adult population samples

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Primary biliary cirrhosis (PBC) is an autoimmune chronic liver disease that is characterized by the progressive destruction of interlobular or septal bile ducts, eventually leading to liver cirrhosis. In the diagnosis of PBC, the presence of antimitochondrial antibody (AMA) is a hallmark. Detection of AMA has been carried out by indirect immune fluorescence (IIF) on cryostat sections of rodent tissues. However, AMA detected by IIF was not always specific for PBC.[1] In some patients positive for AMA, as detected by IIF, the identification of target antigen was needed. PBC-specific AMA was directed to the E2 component of 2-oxo-acid dehydrogenase complexes, including pyruvate dehydrogenase complex (PDC), 2-oxo-glutarate dehydrogenase complex (OGDC), and branched chain 2-oxo-acid dehydrogenase complex (BCOADC) located in the inner membrane of mitochondria.[2–4] Antibodies to the E3 binding protein, E1α and/or E1β, of PDC were also found in the sera of some PBC patients.[3,5] The dominant epitope of PDC with which AMA reacted was the inner lipoyl domain of the E2 component.[6] Various methods are available for the detection of PBC-specific AMA. An immunoblotting assay revealed the molecular species that was reactive with AMA-positive serum. The identification of the target antigens enabled us to detect the antibody by enzyme-linked immunosorbent assay (ELISA), using native 2-oxo-acid dehydrogenase proteins or recombinant 2-oxo-acid dehydrogenase E2 protein, or an enzyme inhibition assay. The usefulness of AMA in the diagnosis of PBC has been established. However, the quantitative measurement of AMA by IIF or ELISA was not a useful predictor of disease progression in patients with PBC.[7] There have been several investigations on the prevalence of AMA detected by IIF or ELISA in non-selected general populations, showing the presence of AMA-positive individuals who had no laboratory or clinical findings suggestive of liver disease.[8–13] These studies raised the important question of whether AMA-positive healthy individuals would eventually develop PBC.

Mitchison et al.[14] reported 29 individuals who were positive for AMA by IIF, but who had no laboratory or clinical signs suggestive of PBC. Twenty-four of the 29 showed histological findings diagnostic of or compatible with PBC, indicating the usefulness of AMA in the diagnosis of the preclinical stage of PBC. Metcalf et al.[15] followed these 29 individuals for a range of 11.0 to 23.9 years. During the follow-up period, 5 of them died, and their deaths were not attributable to liver disease.[15] Twenty-two (76%) developed symptoms of PBC and 24 (83%) had laboratory findings showing cholestasis.[15] Metcalf et al.[15] tested the baseline samples of 27 individuals by ELISA, using the E2 components of PDC and OGDC as antigens, and found 21 individuals positive for these proteins, all of whom had histological findings diagnostic of, or compatible with, PBC.[15] Only one of the 6 patients who tested negative by ELISA had histological findings compatible with PBC, suggesting the importance of evaluating the target antigens of AMA detected by IIF. As reported in this issue of the *Journal of Gastroenterology*, Kisand et al.[16] tested the serum samples of 2144 inhabitants aged 15 to 95 years in small Estonian villages for AMA by ELISA, using native PDC and a recombinant E2 component of PDC, the enzyme inhibition assay and/or IIF. Sixteen individuals, 2 of whom were found to have PBC, tested positive for AMA by ELISA using native PDC and/or recombinant PDC-E2. Eight of the other 14 positive individuals were followed for 9 years. Three of those available for follow-up had abnormal liver test results during the follow-up period. Interestingly, 2 of the 3 subjects who had abnormal liver test results during the follow-up were positive for AMA by IIF on baseline tests, and 1 was positive by IIF during the follow-up period. One individual who

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was positive by IIF on the baseline test, but who did not show abnormal liver test results, had chronic lymphocytic leukemia. Although no patients were examined histologically and the follow-up period was short, this study by Kisand et al. suggested that the IIF test for AMA was sufficient for prediction of the development of PBC.

However, the study by Kisand et al.[16] raised the question as to what the antibody to PDC or PDC-E2 signified. PDC-E2 is a molecule that is well conserved among various species. Sera from patients with PBC were shown to react with human and *Escherichia coli* PDC-E2.[17] Vilagut et al.[18] showed that sera from PBC patients reacted with the 65-kD heat-shock protein (HSP) of *Mycobacterium gordonae* and that a monoclonal antibody to the 65-kD HSP recognized the major mitochondrial antigens of AMA, PDC-E2, and BCOADC-E2. Bacterial infection may induce the production of low titers of antibodies against the E2 component of PDC detected by sensitive ELISA. The cross-reactivity of anti-trifluoroacetyl antibody and anti-lipoic acid antibody with the dominant epitopes of the mitochondrial antigens of AMA suggests that environmental insults initiate the autoimmune response in PBC.[19] Natural autoantibodies to dihydrolipoamide acyltransferase were also reported, although they recognized an epitope different from that recognized in PBC sera.[20] The epitope recognized by AMA varied with time in healthy individuals.[13] This may be explained by antigen determinant spreading. To elucidate the clinical significance of AMA detected by ELISA in healthy individuals, a longer period of follow-up of positive individuals is needed.

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