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Letter to the Editor

Anti-mitochondrial Antibodies in Patients with Elevated Alkaline Phosphatase/Gamma-glutamyl Transferase Levels: Hallmark or Bystander?

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Dear Editors,

I read with great interest the recently published article by Zeng *et al*.[1] They reported that positive primary biliary cholangitis (PBC)-specific antibodies, along with elevated alkaline phosphatase (ALP) and/or gamma-glutamyl transferase (GGT) levels, may occur in various non-PBC diseases.

Elevated ALP and/or GGT levels are commonly encountered in patients with different diseases, and some of these patients may test positive for anti-mitochondrial antibodies (AMA). However, when the elevation of ALP and/or GGT levels can be accounted for by other identifiable etiologies, the diagnosis of PBC should not be established in the absence of histologic evidence.

AMA has been considered the serologic hallmark of PBC. However, AMA reactivity alone is insufficient for diagnosing PBC.[2] The positivity rate of AMA in healthy individuals ranges from 0.1% to 0.8%, which is significantly higher than the reported prevalence of PBC, which varies from 1.91 to 40.2 per 100,000.[3] Li *et al*.[4] reported an AMA-M2 positivity rate of 3.23% among 72,173 individuals undergoing health check-ups. Notably, only 0.6% of these AMA-M2-positive, non-PBC individuals developed PBC after a median follow-up of 6.6 years. Moreover, as reported by Zeng *et al*. and many others, AMA can be detected in patients with non-PBC liver diseases as well as non-liver diseases.

AMA is a non-organ-specific autoantibody targeting mitochondrial membrane structures. Compared with AMA, AMA-M2, along with several antinuclear antibodies (such as anti-sp100, anti-gp210, anti-lamin B receptor, and anti-p62), demonstrates higher specificity for detecting PBC.[5] The detection of these antibodies requires laboratory techniques based on recombinant antigens to avoid low specificity. A previous study reported that the dot blot assay for AMA-M2 was more specific than the enzyme-linked immunosorbent assay used in Zeng *et al*.'s research. However, whether comprehensive detection of antinuclear antibodies and the application of more specific laboratory techniques significantly improve diagnostic accuracy remains unclear.

In Zeng *et al*.'s report, among the non-PBC liver diseases, the most prevalent was metabolic dysfunction-associated fatty liver disease (MAFLD), followed by drug-induced liver injury. MAFLD has become the leading cause of liver disease worldwide and is also a common cause of elevated alanine aminotransferase and GGT levels. Ravi *et al*.[6] reported that four (1%) of 398 patients with MAFLD or alcohol-related liver disease were AMA positive. Among the three AMA-positive patients with available histology, only one, with an AMA titer of 1:640, had minimal bile duct damage but normal ALP, while the other two showed no evidence of PBC. Another study reported a higher AMA positivity rate of 4% in patients with MAFLD who lacked histological evidence of PBC.[7]

GGT is highly sensitive for diagnosing liver injury, yet its specificity is poor. This is because many conditions, such as obesity, smoking, excessive alcohol intake, and medication use without significant liver injury, are associated with elevated GGT. Therefore, GGT is usually measured in combination with ALP for the diagnosis of cholestasis. Both the European Association for the Study of the Liver and the Chinese Society of Hepatology have proposed the criterion for diagnosing cholestatic liver disease: "ALP levels greater than 1.5 times the upper limit of normal and GGT levels exceeding three times the upper limit of normal".[8] In Zeng *et al*.'s report, most patients had elevated GGT but normal ALP levels. This might largely explain why they were not diagnosed with PBC, even though several studies have reported normal ALP levels in PBC patients.[9]

Zeng *et al*. enrolled patients who received treatment targeting primary diseases without ursodeoxycholic acid (UDCA) therapy. Etiological treatment is relatively straightforward for patients with drug-induced liver injuries, since drug discontinuation is the main management strategy, and most patients can fully recover without long-term sequelae. However, the situation is much more challenging for MAFLD patients. Only a minority can achieve the target weight loss of 7–10% through lifestyle interventions alone, and an even

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smaller percentage can maintain this weight loss over time.[10] Thus, I am curious about the percentage of MAFLD patients who achieved the weight loss goal in Zeng *et al*.'s report. Notably, they observed a further increase in ALP and/or GGT levels after etiological treatment in some MAFLD patients. However, only four of these 13 patients underwent liver biopsy at baseline, and none showed histological findings of PBC. Alternative tests to liver biopsy, including controlled attenuation parameter measurement and novel biomarkers, may aid in the diagnosis of MAFLD.

Managing these non-responders, particularly decisions on whether to perform an immediate liver biopsy or initiate appropriate therapies (such as UDCA) for individualized experimental therapy, presents significant challenges. However, when patients exhibit multiple factors associated with an increased risk of PBC, such as being middle-aged females or having elevated immunoglobulin M levels (or levels high within the normal range), a timely liver biopsy to confirm or rule out the diagnosis of PBC is especially advisable.

Some may be concerned about the risk of disease progression if these patients actually have PBC but are not initially treated with UDCA. Even when PBC is present, based on their ALP and bilirubin levels, these patients generally have early-stage PBC. Non-invasive assessment methods, including FibroScan and magnetic resonance elastography, combined with risk scoring systems such as the GLOBE score, can effectively facilitate risk stratification for these individuals. A large-scale Japanese cohort study has shown that delayed UDCA treatment does not affect outcomes in patients with early-stage PBC.[11]

Therefore, for patients with positive AMA, elevated ALP and/or GGT levels, and identifiable alternative etiologies, the practical strategy proposed by Zeng *et al*. effectively minimizes the likelihood of misdiagnosing PBC and reduces the need for liver biopsy. I wish to extend my appreciation to Zeng *et al*. for providing additional evidence that may help reduce the overdiagnosis of PBC. Given that PBC is an incurable condition, overdiagnosis can undoubtedly inflict unnecessary distress on patients.

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Conflict of interest

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Author contributions

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