Optimal testing strategies for incidental anti-mitochondrial M2 antibody-positive patients

 Kristina Emsell-Needham[1], Sujoy Khan[2]

[1]Immunology Laboratory, Scarborough Hull York Pathology Services (SHYPS), Hull Royal Infirmary, Hull, HU3 2JZ, UK; [2]Department of Immunology and Allergy, Castle Hill Hospital, Hull University Teaching Hospitals NHS Trust, HU16 5JQ; UK

Dear Editor,

We read with interest the article by Ilkay Ergenc and colleagues[1] on the significance of incidental anti-mitochondrial M2 pattern (AMA-M2) positivity using indirect immunofluorescence (IIF) in the development of primary biliary cirrhosis (PBC). However, we would like the authors to clarify some results reported in the study.

The authors preferred liver ultrasonography with transient elastography (TE) for screening for fibrosis (being non-invasive). However, only eleven patients with a 'definitive' diagnosis of PBC underwent TE. Clarification is required on the 'definitive' test, as TE identified only eight patients with evidence of fibrosis (>6.2 kPA), accounting for less than a fifth of the patients. The conclusion that one-third of the patients developed PBC over the median 27-month follow-up period therefore requires justification.

We also seek clarification as we confronted two possibilities while trying to construct a 2x2 table (sensitivity and specificity of AMA-M2 IIF) based on the results provided (Fig. 1).

The first possibility: fifteen patients confirmed with a diagnosis of PBC, 23 tested positive without evidence of a PBC diagnosis, 2 patients negative for AMA-M2 with PBC leaves eight patients that are truly negative. Sensitivity and specificity for AMA-M2 IIF calculates to 88% and 25%, respectively.

The second possibility: 21 patients with positive AMA-M2 IIF and 27 who tested negative. As two patients were negative for AMA-M2, this leaves 13 patients with confirmed disease who test positive, 8 patients AMA-M2 positive but no disease, and 25 patients who were truly negative. Using these values, sensitivity and specificity calculate to 86.6% and 75.75%, respectively.

Finally, as IIF interpretation remains subjective, we investigated the utility of IgG/IgM anti-mitochondrial immunoblot assays

First possibility				Second possibility		
	PBC				PBC	
AMA-M2	Positive	Negative		AMA-M2	Positive	Negative
Positive	15	23		Positive	13	8
Negative	2	8		Negative	2	25
		Total = 48				Total = 48
Sensitivity	88	%		Sensitivity	86.6	%
Specificity	25	%		Specificity	75.75	%

Figure 1. 2x2 table constructs.

(M2, M4, and M9) in patients with positive IIF (both typical and atypical patterns on mouse liver/kidney/stomach (LKS) tissue) but negative EUROImmun M2 and M23E immunoblots. Retrospective data analysis of all M2/M4/M9 immunoblots performed between 2014 and 2021 identified 169 samples, of which 51 samples were discrep- ant for immunoblot results. Twenty-one patients had an established diagnosis of PBC, and for all these patients, the mitochondrial M2/ M4/M9 immunoblot assay added no utility to the diagnosis of PBC in addition to the routine analysis of IIF via LKS, reflexed liver immunoblot, immunoglobulin quantitation, liver function tests, and diagnostic imaging. For the remaining 30 patients without a diagnosis of PBC, the mitochondrial M2/M4/M9 blot offered no additional utility.

In conclusion, we agree with the authors that AMA-M2 patients should be under follow-up (as a laboratory comment to reflect the importance of regular liver function tests), but testing strategies should address the cohort of patients who remain at the highest risk of developing the disease.

Reference

1. Ergenc I, Gozaydinoglu B, Keklikkiran C, Yilmaz Y. The risk of development of primary biliary cholangitis among incidental antimitochondrial M2 antibody-positive patients. Hepatol Forum 2023;4(2):69–73. [CrossRef]