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Anti-GP2 IgA: a biomarker for disease severity and/or cholangiocarcinoma in primary sclerosing cholangitis?

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Primary sclerosing cholangitis (PSC) is a heterogeneous and complex syndrome with highly variable disease progression and unknown etiopathogenesis, the latter perhaps influenced by the microbiome.^{1,2} Moreover, it is a premalignant disease in that it confers a significant risk for the development of cholangiocarcinoma (CCA) in a subset of patients.³ Detection of CCA in PSC poses a major diagnostic dilemma as inflammation-related dominant strictures in PSC may mimic malignant strictures.³ Contemporary diagnostic modalities for early detection of CCA in patients with PSC remain suboptimal although innovative approaches are emerging.⁴ Hence, there is a critical need for the development of a biomarker which may identify the subgroup of patients with PSC at risk for CCA. Such a biomarker would enable earlier CCA detection which in turn increases the likelihood of having curative treatment options. Biomarkers, in general, are analytes which can be detected in tissues, cells or body fluids, and signify either the presence of a disease or its outcome.⁵ The ideal biomarker should be readily detected in a non-invasive manner, and be highly sensitive and specific in its diagnostic, predictive and prognostic capability.⁵

In this issue, Jendrek *et al* report a potential biomarker, antiglycoprotein 2 (anti-GP2), in PSC, CCA, as well as secondary sclerosing cholangitis (SSC).⁶ Autoantibodies against glycoproteins of the pancreatic acini (PABs) are reported to have a high specificity for Crohn's disease.⁷ PABs are directed against proteins predominantly expressed in the exocrine pancreas, including glycoprotein 2 (GP2), and the CUB and zona pellucida-like domains-containing protein 1 (CUZD1).⁷ GP2 is known to interact with fimbriated enterobacteria, whereas a distinct biological function of CUZD1 has not been identified.⁷ A recent study demonstrated that both antibodies were more prevalent in Crohn's disease than ulcerative colitis (UC).⁷ Moreover, in data not published, Jendrek *et al* identified the presence of anti-GP2 in three out of nine patients with inflammatory bowel disease (IBD) and concomitant PSC. This preliminary data prompted a larger study examining the utility of anti-GP2 as a potential biomarker in 138 Norwegian patients with PSC. The control groups in this study comprised of healthy controls (n=52) and patients who had UC without PSC (n=62). The validation cohort consisted of 180 German patients with PSC, 56 patients who had CCA without PSC, 20 patients with SSC and 18 patients with autoimmune hepatitis

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(AIH). Sera collected from all patients were assayed for the PABs anti-GP2 IgA and IgG as well as anti-CUZD1 IgA and IgG using indirect immunofluorescence. Anti-GP2 IgA was the only PAB with a high prevalence in patients with PSC compared with healthy controls (52% vs 1.9%, $p<0.001$). The high prevalence of anti-GP2 IgA in patients with PSC was confirmed in the German cohort. Patients who had UC without PSC did not have significant occurrence of anti-GP2 IgA. Furthermore, anti-GP2 IgA was also detected in a significant proportion of patients with CCA without PSC (35.7%), SSC (55%), but not in AIH (5.6%). Interestingly, anti-GP2 IgA positivity in patients with PSC signified the presence of more severe disease with a shorter, liver transplantation-free survival. Additionally, a strong association of anti-GP2 IgA positivity and the presence of CCA was observed in both PSC cohorts. In the Norwegian cohort, 19.7% of anti-GP2 IgA positive patients with PSC had CCA compared with 3.1% of the anti-GP2 IgA negative patients ($p<0.001$). Similarly, in the German cohort, the proportion of patients who had PSC with CCA was 13.1% in anti-GP2 IgA positive patients compared with 4.2% in anti-GP2 IgA negative patients. Although a significant association was noted between anti-GPA IgA positivity and CCA without PSC, a much higher occurrence of anti-GP2 IgA was noted in PSC-associated CCA (35.7% vs 86%, $p<0.001$). Based on a multivariate logistic regression analyses, the association of anti-GP2 IgA positivity with CCA was observed independent of serum bilirubin level, patient age and PSC duration.

Overall, the findings of this cross-sectional study suggest that anti-GP2 IgA identifies patients who had PSC with a distinct, more severe disease phenotype, and with CCA. In this regard, anti-GP2 IgA has the potential to be a cancer biomarker, and hence have utility in identifying a subset of patients who had PSC with existing early cancer or at high risk for subsequently developing biliary tract cancer. These observations, although promising, need to be validated in large prospective studies to more intensely evaluate the role of anti-GP2 IgA as a cancer biomarker in PSC and as an independent predictor of survival in this patient population. Further studies may also elucidate whether the shorter transplantation-free survival noted in patients who had PSC with anti-GP2 IgA is related to the presence of CCA alone or whether anti-GP2 IgA positivity portends a significantly reduced non-cancer related survival as well. Finally, we note that anti-GP2 IgA positivity was present in patients with SSC indicating the antibodies likely occur in response to bile duct injury and are not pathogenic, although they may connote an influence of the microbiome on disease progression.

A limitation of the study is lack of data on carbohydrate antigen 19-9 (CA 19-9), a biomarker often used in CCA surveillance in PSC but with several caveats.⁸⁹ Whether the anti-GP2 IgA has any role as a biomarker for CCA independent of CA 19-9 needs to be carefully examined in further studies. Testing the association between anti-GP2 IgA and the stage of CCA, would also provide critical information to determine the efficacy of anti-GP2 IgA as a biomarker for early detection of CCA. Future studies should also investigate the association between longitudinal trends of anti-GP2 IgA and the risk of development of CCA in a prospective cohort study setting.

Development of highly sensitive and specific assays or methods for detection of biomarkers remains a notable challenge. Jendrek *et al* used indirect immunofluorescence to detect anti-

GP2 IgA. Disadvantages of this technique include potential for cross-reactivity, high background and autofluorescence interfering with detection. Many of these limitations can be overcome with the use of more specific assays such as ELISA.

In conclusion, Jendrek *et al*/have identified an association between anti-GP2 IgA and biliary tract diseases including PSC, SSC and PSC with CCA. Anti-GP2 IgA has the potential to be a biomarker for disease severity in PSC and PSC-associated CCA, and as such may have utility in early detection of CCA in a subset of patients with PSC. The study overall represents an essential first-step in describing a novel biomarker in a premalignant disease where early detection of malignancy remains a conundrum. Essential next steps include validation of these findings with prospective studies using methods with higher specificity and sensitivity in detection of anti-GP2 IgA.

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