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A Novel Antibody Associated with Autoimmune Pancreatitis

TO THE EDITOR: Frulloni et al. (Nov. 26 issue)¹ report on a new serologic marker for autoimmune pancreatitis. A total of 5 of 110 patients with pancreatic cancer had a positive test for antibodies, with a sensitivity of 94%. I agree with the authors that this is an imperfect test to rule out the diagnosis. Were the levels of IgG4 normal in these five patients? Perhaps the diagnostic value of the antibody test could be improved if it were combined with the IgG4 levels.

Also, there is increasing evidence that autoimmune pancreatitis is a risk factor for pancreatic cancer.² For example, a recent study by Kamisawa et al. showed a high frequency of *K-ras* mutations in autoimmune pancreatitis.³ In reviewing these five cases, is there histopathologic evidence of autoimmune pancreatitis? It might be that the presumed false positive antibody tests were in fact markers of an underlying autoimmune pancreatitis.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Frulloni et al. identify an antibody against plasminogen-binding protein (PBP) of *Helicobacter pylori* in most patients with autoimmune pancreatitis and in 5% of patients with pancreatic cancer. Their findings not only help to discriminate autoimmune pancreatitis from pancreatic cancer but also provide a link between *H. pylori* infection and autoimmune pancreatitis. However, two issues deserve discussion. First, although healthy controls were not positive for

anti-PBP antibodies, patients with active *H. pylori* infection may have had false positive results. Therefore, the authors should have enrolled another control group of patients with *H. pylori* infection to validate the diagnostic accuracy of this assay. Second, *H. pylori* has been suggested as a cause of autoimmune pancreatitis,^{1,2} and the authors found a homology between the peptide AIP₁₋₇ and the PBP of *H. pylori*. To clarify the role of *H. pylori* in the pathogenesis of autoimmune pancreatitis, they should describe the status of *H. pylori* infection in the patients with autoimmune pancreatitis and pancreatic cancer.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Frulloni et al. report the identification of anti-PBP peptide antibodies associated with autoimmune pancreatitis. We have concerns about this study. In a previous article by Frulloni and colleagues,¹ from January 2000 through March 2008, a total of 58 patients received a diagnosis of autoimmune pancreatitis. However, in this study, from January 2002 through November 2008, serum samples were obtained from only 20 patients with autoimmune pancreatitis. Even though data on the validation group may have been derived from the same study periods, serologic findings in a substantial portion of the entire cohort may not have been evaluated. Therefore, the selectively accrued cohort may lead to

conflicting results in external validation studies. The previous study by Frulloni et al.¹ might have included a fair proportion of patients with idiopathic duct-centric chronic pancreatitis,² and this result suggests that the anti-PBP peptide antibodies might be related to idiopathic duct-centric chronic pancreatitis rather than autoimmune pancreatitis. Because the IgG1 immune complex may be related to both IgG4-negative autoimmune pancreatitis and idiopathic duct-centric chronic pancreatitis,³ further detailed comments on the subtype of IgG antibodies against the PBP peptide may be needed to elucidate the role of this antibody in autoimmune pancreatitis.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Landman asks whether the IgG4 levels in the five patients with pancreatic cancer and a positive antibody test were normal, suggesting that cancer may have arisen from previously undiagnosed autoimmune pancreatitis. In these five patients, the IgG4 levels were normal. We are reviewing the five cases to evaluate the possibility that these patients might have had previously undiagnosed autoimmune pancreatitis.

Combining antibody testing and IgG4 levels may improve the diagnostic value, since among the patients with autoimmune pancreatitis, 2 patients who were negative for anti-PBP peptide antibodies had elevated IgG4 levels and 16 patients with normal IgG4 levels had a positive antibody test. Prospective studies may confirm the clinical usefulness of the combined serologic tests.

Wang and Kao suggest that the patients with active *H. pylori* infection may have had false posi-

tive results for anti-PBP peptide antibodies. We believe the possibility of false positive results in subjects with active *H. pylori* infection is quite remote, since the response to the described epitope of PBP protein was limited mainly to patients with autoimmune pancreatitis and possibly related to a particular genetic background. Indeed, previous observations suggest that the immune response to an infectious agent in a particular autoimmune disease involves the presence of a subgroup of antibodies directed against a particular epitope. Such a response is not detected in normal subjects and in patients with other autoimmune diseases.^{1,2} However, at the beginning of the study, we did not know that the identified AIP peptide shared a homology with an *H. pylori*-derived protein. Therefore, we cannot say whether the patients with autoimmune pancreatitis and pancreatic cancer in our study had active *H. pylori* infection.

Park et al. are concerned about the selection of patients considered in this study. The patients enrolled were consecutive. The numbers of patients are smaller than in the previous study because the period is slightly different and some patients were observed more than 1 month after the clinical onset of the disease and were not included.

Experts from the United States and Europe consider idiopathic duct-centric chronic pancreatitis to be a type II form of autoimmune pancreatitis³ on the basis of clinical, radiologic, and pathological findings and, in particular, on the basis of a similar response to corticosteroids. The estimated prevalence of type II autoimmune pancreatitis in Italy, based on surgical specimens, is 40%.⁴ Therefore, we disagree that anti-PBP peptide antibodies might be related to idiopathic duct-centric chronic pancreatitis. We are analyzing the IgG subtype of anti-PBP peptide antibodies; however, we doubt that this analysis will elucidate the role of the antibody in autoimmune pancreatitis.

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Since publication of their article, the authors report no further potential conflict of interest.

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Rituximab, B-Lymphocyte Depletion, and Beta-Cell Function

TO THE EDITOR: Pescovitz et al. (Nov. 26 issue)¹ reported that the use of B-lymphocyte depletion therapy with rituximab was effective in preserving beta-cell function in patients with newly diagnosed type 1 diabetes who did not have severe infections. B cells may play a role in preventing infection *in vivo* by taking up a specific pathogen when it enters the bloodstream. This event is followed by the presentation of the specific antigen to T cells, which increases the level of T-cell response to better control overwhelming infection; this sequence of events does not occur in response to local infections. In addition, since studies of B-cell knockout in autoimmune mice with diabetes have shown that T-cell response to islet cells (insulinitis) is minimal, even in the presence of efforts to prevent the development of diabetes,^{2,3} it follows that the cessation of rituximab therapy may induce autoreactive T cells to attack pancreatic beta cells. Thus, it is important to watch for the complications of severe infections^{4,5} and, in the long-term, for appropriate beta-cell function when using rituximab in the treatment of patients with newly diagnosed type 1 diabetes.

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THE AUTHORS REPLY: We agree with Nagafuchi and colleagues that when patients with newly diagnosed diabetes are treated with rituximab, long-term follow-up is essential to rule out increased rates of infection and other adverse events. We acknowledged the long-term risk of unknown adverse events in our article and for this reason recommended that the use of such therapy should be limited to carefully controlled studies. Although the potential for an augmented response at the time of reconstitution is reasonable, such an event did not occur in models of nonobese mice with diabetes that were given anti-CD20 treatment.^{1,2} Furthermore, we found that the rate of C-peptide loss did not accelerate with recovery of B cells between 6 months and 1 year into our study. Consequently, such a concern was not supported by experimental evidence.

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Since publication of their article, the authors report no further potential conflict of interest.

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