PANCREAS NEWS

Autoimmune Pancreatitis, Pancreatic Cancer and Immunoglobulin-G4

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The occurrence of pancreatic cancer associated with autoimmune pancreatitis (AIP) has sometimes been reported [1, 2, 3, 4]. Of the four cases reported, pancreatic cancer was diagnosed simultaneously with AIP in two cases [1, 4]; one case of pancreatic cancer developed five years after a pancreaticoduodenectomy for AIP [2] and in the other case, the pancreatic cancer developed three years after steroid therapy was begun [3]. The possibility that pancreatic cancer may develop in AIP patients has recently been pointed out by Kamisawa *et al*. [5]. These authors assessed the possible relationship between AIP and pancreatic cancer by analyzing the K-*ras* mutation in the pancreatobiliary tissue of patients with AIP and they found a significant K-*ras* mutation in the pancreatobiliary region of patients with AIP suggesting that autoimmune pancreatitis may be a risk factor for pancreatobiliary cancer.

On the basis of these observations, it is important to evaluate a biological marker of autoimmune pancreatitis, such as immunoglobulin G4 (IgG4), and to evaluate whether IgG4 is useful in the differential diagnosis between AIP and pancreatic cancer. We should remember that it has recently been shown that IgG4 serum levels do not have a good specificity for this purpose [6]. A new test has recently been developed [7] by an Italian group. To identify pathogenetically relevant autoantigen targets, the authors screened a random peptide sampling with pooled IgG obtained from 20 patients with autoimmune pancreatitis. Peptide-specific antibodies were detected in serum specimens obtained from the patients. Among the peptides detected, peptide AIP(1-7) was recognized by the serum specimens from 18 of 20 patients with autoimmune pancreatitis and by serum specimens from 4 of 40 patients with pancreatic cancer, but not by serum specimens from healthy controls. The peptide showed homology with an amino acid sequence of the plasminogen-binding protein (PBP) of *Helicobacter pylori* and with ubiquitin-protein ligase E3 component n-recognin 2 (UBR2), an enzyme highly expressed in acinar cells of the pancreas. Antibodies against the PBP peptide were detected in 19 of 20 patients with autoimmune pancreatitis (95.0%) and in 4 of 40 patients with pancreatic cancer (10.0%). Such reactivity was not detected in patients with alcohol-induced chronic pancreatitis or intraductal papillary mucinous neoplasms. The results were also validated in another series of patients with autoimmune pancreatitis or pancreatic cancer; 14 of 15 patients with autoimmune pancreatitis (93.3%) and 1 of 70 patients with pancreatic cancer (1.4%) had a positive test for anti-PBP peptide antibodies. When the test and validation groups were combined, the test was positive in 33 of 35 patients with autoimmune pancreatitis (94.3%) and in 5 of 110 patients with pancreatic cancer (4.5%). In conclusion, this marker is also an imperfect test for distinguishing AIP from pancreatic cancer. Serum leptin has also been proposed as marker to differentiate autoimmune pancreatitis from pancreatic cancer [8]; however, in this study, the number of AIP patients was quite low and these promising results should be confirmed in a larger population. At present, a possible method for distinguishing AIP from pancreatic cancer come from the study of Song *et al*. [9]. These authors aimed at determining whether the combined measurement of total IgG and IgG4 could increase the diagnostic sensitivity for AIP while maintaining specificity as compared to IgG4 alone. They prospectively measured total serum IgG and IgG4 together in 82 consecutive patients with AIP, and

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Abbreviations AIP: autoimmune pancreatitis; PBP: plasminogen-binding protein

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seropositivity was defined as the elevation of either total IgG or IgG4. To evaluate specificity in the differentiation of AIP from pancreatic cancer, total serum IgG and IgG4 were prospectively measured in 110 patients with pancreatic cancer. These authors found that, in patients with AIP, the sensitivity of IgG4 (equal to or greater than 135 mg/dL) was 52.4% (43/82), significantly higher than that (46.3%, 38/82) of total IgG (equal to or greater than 1,800 mg/dL) ($P<0.05$). The sensitivity of the combined measurement of total IgG and IgG4 for AIP was 68.3% (56/82), significantly higher than that of IgG4 alone ($P<0.05$). The specificity of total IgG and IgG4 in the differentiation of AIP from pancreatic cancer was 96.4% and 99.1%, respectively. The specificity of the combined measurement of total IgG and IgG4 was 95.5%, and it was not significantly different from that of IgG4 alone ($P=0.125$). The conclusion of this paper was that the combined measurement of total serum IgG and IgG4 may increase diagnostic sensitivity without sacrificing specificity as compared to IgG4 alone.

The search for a serological marker capable of differentiating AIP from pancreatic cancer continues, but the road seems to be long.

Conflict of interest The authors have no potential conflicts of interest

References

1. Inoue H, Miyatani H, Sawada Y, Yoshida Y. A case of pancreas cancer with autoimmune pancreatitis. Pancreas 2006; 33:208-9. [PMID 16868495]

2. Ghazale A, Chari S. Is autoimmune pancreatitis a risk factor for pancreatic cancer? Pancreas 2007; 35:376. [PMID 18090248]

3. Fukui T, Mitsuyama T, Takaoka M, Uchida K, Matsushita M, Okazaki K. Pancreatic cancer associated with autoimmune pancreatitis in remission. Intern Med 2008; 47:151-5. [PMID 18239323]

4. Witkiewicz AK, Kennedy EP, Kennyon L, Yeo CJ, Hruban RH. Synchronous autoimmune pancreatitis and infiltrating pancreatic ductal adenocarcinoma: case report and review of the literature. Hum Pathol 2008; 39:1548-51. [PMID 18619645]

5. Kamisawa T, Tsuruta K, Okamoto A, Horiguchi S, Hayashi Y, Yun X, et al. Frequent and significant K-ras mutation in the pancreas, the bile duct, and the gallbladder in autoimmune pancreatitis. Pancreas 2009; 38:890-5. [PMID 19752775]

6. Morselli-Labate AM, Pezzilli R. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: A systematic literature review and meta-analysis. J Gastroenterol Hepatol 2009; 24:15-36. [PMID 19067780]

7. Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, et al. Identification of a novel antibody associated with autoimmune pancreatitis. N Engl J Med 2009; 361:2135-42. [PMID 19940298]

8. Pezzilli R, Barassi A, Corsi MM, Morselli-Labate AM, Campana D, Casadei R, et al. Serum leptin, but not adiponectin and receptor for advanced glycation end products, is able to distinguish autoimmune pancreatitis from both chronic pancreatitis and pancreatic neoplasms. Scand J Gastroenterol 2010; 45:93-9. [PMID 19883273]

9. Song TJ, Kim MH, Moon SH, Eum JB, Park DH, Lee SS, et al. The combined measurement of total serum IgG and IgG4 may increase diagnostic sensitivity for autoimmune pancreatitis without sacrificing specificity, compared with IgG4 alone. Am J Gastroenterol 2010 (advance online publication, December 15, 2009). [PMID 20010924]