IgG4 as a Serological Marker of Autoimmune Pancreatitis: The Latest News

Raffaele Pezzilli, Roberto Corinaldesi

Department of Internal Medicine, Sant'Orsola-Malpighi Hospital. Bologna, Italy

After standard laboratory and imaging studies no causes are identified in nearly 30% of chronic pancreatitis. Japanese authors have helped us to decrease the percentage of so-called idiopathic pancreatitis because they have identified a new clinical entity of pancreatitis: the autoimmune pancreatitis [1]. In the past few years, the frequency of new diagnoses of pancreatitis due to this new entity has increased in Japan and in Europe [2] as well as in other Eastern countries [3]. An autoimmune pathogenesis has been proposed because this condition is occasionally associated with antibodies or other autoimmune-associated diseases, such as Sjogren syndrome, primary biliary cirrhosis and inflammatory bowel disease [1, 4, 5, 6]. Idiopathic fibrosclerosing disorders such as primary sclerosing cholangitis, retroperitoneal fibrosis, Riedel thyroiditis and orbital pseudotumors have been also reported, associated with a clinical picture compatible with autoimmune pancreatitis [7, 8]; finally, autoimmune pancreatitis has been hypothesized during the course of sarcoidosis [9]. Autoimmune pancreatitis is characterized by diffuse or focal pancreatic swelling with narrowing of the pancreatic duct and/or common bile duct [10]. The histological hallmark of this type of pancreatitis is lymphoplasmocytic infiltration especially concentrated on the pancreatic ducts [4, 8, 11]. Even if an operation is often carried out as a consequence of a diagnosis of pancreatic cancer, treatment with corticosteroids is often effective [12]; thus, differentiation between autoimmune pancreatitis and pancreatic cancer remains a diagnostic challenge which needs to be resolved in the next few years. The answer to this question came from Kamisawa et al. [13]. In their study, the authors sought to clarify the clinical and radiological features of autoimmune pancreatitis in order to differentiate this disease from pancreatic carcinoma more easily; they studied 17 cases initially suspected of having pancreatic carcinoma and found that the patients were predominantly elderly men who frequently presented with jaundice but without the features of acute pancreatitis. Diffuse enlargement of the pancreas and irregular narrowing of the main pancreatic duct were radiologically characteristic; however, segmental swelling and narrowing were detected in seven and two patients, respectively. In segmental cases, neither atrophy of the distal pancreas nor marked upstream dilation of the distal main pancreatic duct was observed; angiographic abnormalities occurred in 54% of the cases. Stenosis of the bile duct was also present in the vast majority of the patients (94% of the cases). Regarding the serological markers, elevation of serum gamma globulins and IgG along with the presence of autoantibodies were usually evident, whereas serum tumor markers were elevated in 54% of the cases. The importance of serologic markers for autoimmune pancreatitis has also been pointed out by Hamano et al. [14]. In this
paper, the authors reported that elevated serum levels of IgG4 are the hallmark of sclerosing pancreatitis. They had previously identified a polyclonal band in the rapidly migrating fraction of gamma globulins in the serum of some patients with sclerosing pancreatitis. Immunoprecipitation assays confirmed that this band was caused by high serum concentrations of the IgG4 fraction of gamma globulins. IgG4 is the rarest of the IgG subclasses and accounts for only 3 to 6% of total IgG in the serum of human subjects. It is unique among the IgG subclasses in its inability to bind C1q complement and, thus, activate the complement pathway and in its low affinity for target antigen. High serum IgG4 concentrations have also been found in a small number of pathological conditions such as atopic dermatitis [15], parasitic disease [16], pemphigus vulgaris and foliaceus [17]. Hamano et al. [14] found that the median serum IgG4 concentrations in the patients with sclerosing pancreatitis were significantly higher than in normal subjects. Furthermore, the serum concentrations of IgG4 in patients with pancreatic cancer, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis and Sjögren syndrome were similar to those of healthy subjects. Finally, they found that treatment with steroids was able to significantly decrease the serum concentrations of IgG4. From these results, the authors concluded that serum IgG4 determination provided a useful means of distinguishing sclerosing pancreatitis from other disorders of the pancreas or biliary tract. More recently, an important confirmatory study has been carried out by Hirano et al. [18]. They reviewed the clinical, radiological and laboratory aspects of 138 patients with a pancreatic mass lesion; 17 of these 138 were not diagnosed initially despite numerous examinations; the serum IgG4 levels were elevated in seven of these and their biopsy specimens had a similar appearance to those of autoimmune pancreatitis; thus, the authors felt that they should be diagnosed as autoimmune pancreatitis or conditions related to autoimmune pancreatitis. Among the 10 patients without elevated IgG4, four patients were eventually diagnosed as having pancreatic cancer during long-term follow-up, one patient was diagnosed as having non-functioning islet cell tumor, four patients were diagnosed as having tumors associated with chronic pancreatitis, and, most importantly, one patient was diagnosed as having autoimmune pancreatitis with sclerosing cholangitis because diffuse narrowing of the main pancreatic duct and multiple strictures of the intrahepatic bile duct were confirmed on ERCP; in this patient, IgG4 rose six months later, the first normal serum IgG4 determination. The finding of late elevation IgG4 in this latter patient emphasizes the need for IgG4 levels to be repeated in the follow-up period in those cases in whom autoimmune pancreatitis is strongly suspected. The study of Hirano et al. [18] further support the usefulness of determining serum IgG4 in order to confirm the diagnosis of autoimmune pancreatitis and to avoid unnecessary surgical procedures for the suspicion of pancreatic cancer; this serum marker seems to also be useful for the follow-up of patients treated with steroids. There is only one need; developing an accepted method for measuring IgG4 in serum and to make it widely available commercially is urgently needed.

Keywords Autoimmune Diseases; Biological Markers; Immunoglobulin G; Pancreatitis

Correspondence
Raffaele Pezzilli
Dipartimento di Medicina Interna
Ospedale Sant'Orsola-Malpighi
Via G. Massarenti, 9
40138 Bologna
Italy
Phone: +39-051.636.4148
Fax: +39-051.549.653
E-mail address: pezzilli@aosp.bo.it

References
1. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of


