

## HIGH SERUM IgG4 CONCENTRATIONS IN PATIENTS WITH SCLEROSING PANCREATITIS

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### ABSTRACT

**Background** Sclerosing pancreatitis is a unique form of pancreatitis that is characterized by irregular narrowing of the main pancreatic duct, lymphoplasmacytic inflammation of the pancreas, and hypergammaglobulinemia and that responds to glucocorticoid treatment. Preliminary studies suggested that serum IgG4 concentrations are elevated in this disease but not in other diseases of the pancreas or biliary tract.

**Methods** We measured serum IgG4 concentrations using single radial immunodiffusion and an enzyme-linked immunosorbent assay in 20 patients with sclerosing pancreatitis, 20 age- and sex-matched normal subjects, and 154 patients with pancreatic cancer, ordinary chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Sjögren's syndrome. Serum concentrations of immune complexes and the IgG4 subclass of immune complexes were determined by means of an enzyme-linked immunosorbent assay with monoclonal rheumatoid factor.

**Results** The median serum IgG4 concentration in the patients with sclerosing pancreatitis was 663 mg per deciliter (5th and 95th percentiles, 136 and 1150), as compared with 51 mg per deciliter (5th and 95th percentiles, 15 and 128) in normal subjects ( $P < 0.001$ ). The serum IgG4 concentrations in the other groups of patients were similar to those in the normal subjects. In patients with sclerosing pancreatitis, serum concentrations of immune complexes and the IgG4 subclass of immune complexes were significantly higher before glucocorticoid therapy than after four weeks of such therapy. Glucocorticoid therapy induced clinical remissions and significantly decreased serum concentrations of IgG4, immune complexes, and the IgG4 subclass of immune complexes.

**Conclusions** Patients with sclerosing pancreatitis have high serum IgG4 concentrations, providing a useful means of distinguishing this disorder from other diseases of the pancreas or biliary tract. (N Engl J Med 2001;344:732-8.)

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**I**N developed countries, most patients with chronic pancreatitis have a long history of alcohol abuse. Alcohol-induced chronic pancreatitis is characterized by recurrent attacks of abdominal pain, irregular dilatation of the pancreatic duct with stone formation, atrophy of the pancreatic parenchyma, and pancreatic exocrine and endocrine insufficiency. A unique form of chronic pancreatitis characterized by infrequent attacks of abdominal pain,

irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma has been described. It has been referred to as sclerosing pancreatitis,<sup>1</sup> primary inflammatory pancreatitis,<sup>2,3</sup> lymphoplasmacytic sclerosing pancreatitis,<sup>4</sup> autoimmune pancreatitis,<sup>5-8</sup> chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct,<sup>9</sup> and sclerosing pancreaticocholeangitis.<sup>10</sup> Sclerosing pancreatitis, the term used in this article, is associated with lymphoplasmacytic inflammation of the pancreas and hypergammaglobulinemia and responds to glucocorticoid treatment. It can be mistaken for pancreatic cancer on endoscopic retrograde cholangiopancreatography or other imaging studies.<sup>1,4,5,7,9,10</sup> The clinicopathologic features of sclerosing pancreatitis mimic those of pancreatitis associated with Sjögren's syndrome, primary biliary cirrhosis, and primary sclerosing cholangitis.<sup>11-15</sup>

We previously found that the serum of some patients with sclerosing pancreatitis had a polyclonal band in the rapidly migrating fraction of gamma globulins. Immunoprecipitation assays confirmed that this band was caused by a high serum concentration of the IgG4 fraction of gamma globulins. IgG4 is the rarest of the IgG subclasses and accounts for only 3 to 6 percent of total IgG in the serum of normal subjects. It is unique among the IgG subclasses in its inability to bind C1q complement and, therefore, activate the classic pathway of complement<sup>16</sup> and in its low affinity for target antigen. Because high serum IgG4 concentrations are found in only a limited number of conditions, such as atopic dermatitis,<sup>17</sup> some parasitic diseases,<sup>18</sup> and pemphigus vulgaris and pemphigus foliaceus,<sup>19</sup> we sought to determine whether serum IgG4 concentrations are high in patients with sclerosing pancreatitis but not in patients with other diseases of the pancreas or biliary tract.

### METHODS

#### Study Subjects

Between September 1994 and February 1999, we obtained serum samples from 20 patients with sclerosing pancreatitis, 15 men and 5 women, who were 38 to 73 years of age (mean [ $\pm$ SD] age, 61  $\pm$  11). We also obtained serum samples from 20 age- and sex-matched

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normal subjects and 45 patients with ordinary chronic pancreatitis (alcoholic in 36 cases and idiopathic in 9 cases), 70 patients with pancreatic cancer, 20 patients with primary biliary cirrhosis, 8 patients with primary sclerosing cholangitis, and 11 patients with Sjögren's syndrome. All serum samples were stored at  $-20^{\circ}\text{C}$ .

All 20 patients with sclerosing pancreatitis had irregular narrowing of the main pancreatic duct and sonolucent swelling of the pancreas that responded to glucocorticoid treatment, obstructive jaundice, hypergammaglobulinemia, and high serum IgG concentrations; 4 patients had high serum IgE concentrations.<sup>2,5,7,8,14</sup> The condition of all 20 patients improved after treatment with 40 mg of prednisolone per day for four weeks, followed by a gradual reduction of 5 mg per week over a period of seven weeks until a daily dose of 5 mg was reached. The patients were followed for 10 to 63 months after treatment was discontinued. Two patients had recurrences of their pancreatitis.

All 45 patients with ordinary chronic pancreatitis had either marked irregular dilatation of the main pancreatic duct or marked calcification of the pancreas,<sup>20</sup> features that were not found in patients with sclerosing pancreatitis. The diagnosis of primary biliary cirrhosis was confirmed by histologic evaluation of liver-biopsy specimens. The diagnosis of primary sclerosing cholangitis was confirmed by cholangiographic examination and liver biopsy. The diagnosis of Sjögren's syndrome was confirmed by the finding of diminished function of the lacrimal and salivary glands and by the presence of Sjögren's syndrome A and Sjögren's syndrome B antibodies in serum. The diagnosis of pancreatic cancer was confirmed on the basis of histologic findings in 26 patients and on the basis of both typical findings on imaging procedures and the clinical course in 44 patients.

All subjects provided written informed consent for invasive tests such as endoscopic retrograde cholangiopancreatography and liver biopsy. This retrospective analysis was not reviewed by an institutional review committee, but all tests and treatments were performed in accordance with institutional guidelines.

### Laboratory Tests

Because there is no widely accepted method of measuring the concentrations of subclasses of IgG, we measured serum IgG4 and the other subclasses of IgG in the patients with sclerosing pancreatitis and the normal subjects using two methods: single radial immunodiffusion (Binding Site, Birmingham, United Kingdom) and enzyme-linked immunosorbent assay (ELISA)<sup>21</sup> (Yoshitomi Pharmaceutical Industries, Osaka, Japan). We found a close correlation between the results of single radial immunodiffusion and those of ELISA for each serum IgG subclass. Serum IgG4 concentrations in the other patients were measured by single radial immunodiffusion. Serum total IgG, IgA, and IgM concentrations were measured by turbidimetric immunoassay, and serum IgE concentrations were measured by ELISA. We determined the cutoff values for serum IgG4 and IgG by analyzing receiver-operating-characteristic curves.

We measured circulating immune complexes with an ELISA kit with monoclonal rheumatoid factor (Immune complex mRF Nissui, Nissui Pharmaceutical, Tokyo, Japan).<sup>22</sup> We used the manufacturer's recommended cutoff value, which was the mean plus 2 SD of values in normal subjects. To detect circulating immune complexes containing IgG4, we designed a new ELISA system using monoclonal rheumatoid factor-coated plates and peroxidase-labeled antihuman IgG4 antibody (AU009, Binding Site) as a tracer antibody. This antihuman IgG4 antibody was the same as that used in single radial immunodiffusion for IgG4. The serum samples were treated with EDTA solution according to the instructions for the circulating immune-complex-assay system. Peroxidase-labeled antihuman IgG4 antibody was diluted 1:5000 with phosphate-buffered saline containing 0.5 percent bovine serum albumin, and specimens were stained with 3,3',5,5'-tetramethylbenzidine (Behring Diagnostics, Marburg, Germany). Optical density was measured at 450 nm with a microplate reader (Bio-Rad Laboratories, Hercules, Calif.). We tentatively defined the cutoff value for the serum concentration

of the IgG4 subclass of immune complexes as an optical-density unit of 0.1, because serum samples from all 20 normal subjects had lower values.

### Statistical Analysis

Statistical analyses were performed with the Mann-Whitney test to compare the serum concentrations of each IgG subclass, IgA, IgM, and IgE in patients with sclerosing pancreatitis with those in normal subjects. The Wilcoxon matched-pairs signed-rank test was used to compare serum IgG concentrations, serum IgG4 concentrations, the ratio of serum IgG4 to serum IgG, serum concentrations of circulating immune complexes, and serum concentrations of the IgG4 subclass of circulating immune complexes in patients with sclerosing pancreatitis before and after four weeks of glucocorticoid therapy. Data were analyzed with the use of SPSS software (version 6.1, SPSS, Chicago).<sup>23</sup> All reported P values are two-sided. To differentiate sclerosing pancreatitis from other pancreatic diseases (ordinary chronic pancreatitis and pancreatic cancer), we analyzed receiver-operating-characteristic curves for serum IgG and IgG4 values with the use of the statistical software package Stat Flex (version 5.0, Artech, Osaka, Japan).<sup>24,25</sup>

## RESULTS

According to both assay methods, the patients with sclerosing pancreatitis had serum IgG4 concentrations that were significantly higher than those in the normal subjects ( $P < 0.001$ ) (Table 1). The patients with sclerosing pancreatitis also had slightly but significantly higher serum IgG1 concentrations and lower serum IgG2 concentrations as determined by ELISA but not by single radial immunodiffusion. There were no significant differences between these two groups with respect to the concentrations of other serum IgG subclasses or of serum IgA, IgM, or IgE (Table 1).

The results of measurements of serum IgG4 and total IgG in the patients with sclerosing pancreatitis and the other groups are shown in Figure 1. Serum IgG4 concentrations were elevated only in the patients with sclerosing pancreatitis (Fig. 1A). Although serum total IgG concentrations were slightly higher in the patients with sclerosing pancreatitis, there was considerable overlap with the other groups (Fig. 1B). The use of a cutoff value for serum IgG4 concentrations of 135 mg per deciliter resulted in a high rate of accuracy (97 percent), sensitivity (95 percent), and specificity (97 percent) for the differentiation of sclerosing pancreatitis from pancreatic cancer. The respective values for the use of a cutoff value of 1883 mg per deciliter for serum IgG were 80 percent, 65 percent, and 81 percent.

To determine the relation between serum IgG4 concentrations and disease activity in patients with sclerosing pancreatitis, we measured serum IgG4 in 12 patients after four weeks of glucocorticoid therapy. All of the patients had remission of symptoms and resolution of abnormalities on imaging studies after four weeks of treatment (Fig. 2). Both the serum IgG4 concentration and the serum IgG4:IgG ratio were significantly lower than their respective base-line values (Table 2); there was also a significant decrease in the median serum IgG concentration. These findings sug-

**TABLE 1.** AGE, SEX, AND SERUM IMMUNOGLOBULIN CONCENTRATIONS OF NORMAL SUBJECTS AND PATIENTS WITH SCLEROSING PANCREATITIS.\*

CHARACTERISTIC	NORMAL SUBJECTS (N=20)	PATIENTS WITH SCLEROSING PANCREATITIS (N=20)	P VALUE†
Age — yr	61±11	61±11	1.00
Male sex — no. (%)	15 (75)	15 (75)	1.00
	median (5th, 95th percentiles)		
Serum IgG1 — mg/dl			
Single radial immunodiffusion	664 (498, 1036)	868 (401, 1784)	0.25
ELISA	859 (698, 1077)	1095 (464, 1991)	0.03
Serum IgG2 — mg/dl			
Single radial immunodiffusion	592 (403, 902)	617 (330, 1234)	0.99
ELISA	510 (326, 726)	366 (263, 639)	0.03
Serum IgG3 — mg/dl			
Single radial immunodiffusion	34 (3, 100)	53 (13, 174)	0.12
ELISA	38 (11, 76)	51 (17, 101)	0.38
Serum IgG4 — mg/dl			
Single radial immunodiffusion	51 (15, 128)	663 (136, 1150)	<0.001
ELISA	41 (14, 156)	597 (24, 1230)	<0.001
Serum IgA — mg/dl‡	247 (144, 392)	226 (85, 552)	0.44
Serum IgM — mg/dl‡	142 (73, 221)	91 (40, 236)	0.11
Serum IgE — IU/ml§	79 (10, 240)	176 (62, 405)	0.09

\*Plus-minus values are means ±SD. ELISA denotes enzyme-linked immunosorbent assay.

†The Mann-Whitney test was used to calculate two-sided P values.

‡A turbidimetric immunoassay was used to measure serum IgA and IgM concentrations.

§An enzyme-linked immunosorbent assay was used to measure serum IgE concentrations. To convert values to micrograms per liter, multiply by 2.4.

gest that the change in the serum IgG4 concentration is a specific effect of glucocorticoid treatment, not a nonspecific effect of treatment on the overall production of immunoglobulins.

To examine whether the high serum IgG4 concentrations were related to high serum concentrations of immune complexes and the IgG4 subclass of immune complexes, we measured these concentrations before and after four weeks of glucocorticoid therapy in 12 patients with sclerosing pancreatitis. The serum concentrations of immune complexes before treatment exceeded the cutoff value of 4.2  $\mu\text{g}$  per milliliter in 92 percent of the patients with sclerosing pancreatitis. The concentrations decreased significantly after four weeks of glucocorticoid therapy (Table 2). Similar to the serum concentration of immune complexes, the serum concentration of the IgG4 subclass of immune complexes was elevated in 92 percent of the patients with sclerosing pancreatitis before therapy and decreased significantly after four weeks of therapy (Table 2).

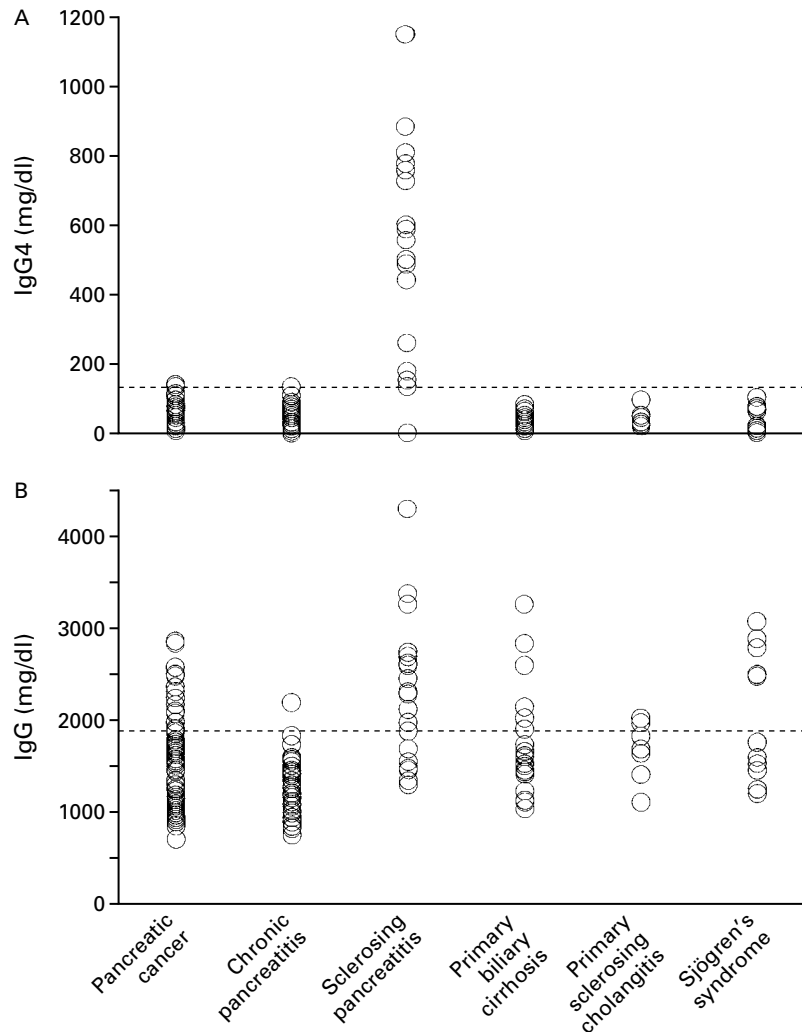
## DISCUSSION

We found high serum IgG4 concentrations in patients with sclerosing pancreatitis but not in patients with ordinary chronic pancreatitis, primary biliary cir-

rhosis, primary sclerosing cholangitis, or Sjögren's syndrome. These findings suggest that sclerosing pancreatitis differs immunologically from these other diseases and that it is a distinct disease entity.

If sclerosing pancreatitis is misdiagnosed, patients may be assumed to have pancreatic cancer and may undergo unnecessary surgery.<sup>1,4,5,7,9,10</sup> At least 5 percent of patients who undergo surgery for cancer of the head of the pancreas are found to have benign inflammatory disease,<sup>26</sup> which may include sclerosing pancreatitis. We found that measurements of serum IgG4 can be used to distinguish sclerosing pancreatitis from pancreatic cancer. Our findings suggest that increased awareness of sclerosing pancreatitis as a discrete entity and the measurement of serum IgG4 in patients suspected of having pancreatic cancer may help reduce the incidence of unnecessary surgery.

In conditions associated with high serum IgG4 concentrations, the IgG4 subclass is usually categorized as a pathologic antibody. In patients with atopic dermatitis, asthma, and some parasitic diseases, high serum concentrations of IgE and IgG4 are a direct response to exogenous antigen,<sup>17,18</sup> and the increase in serum IgG4 antibodies has been postulated to block the access of soluble antigens to IgE-coated mast



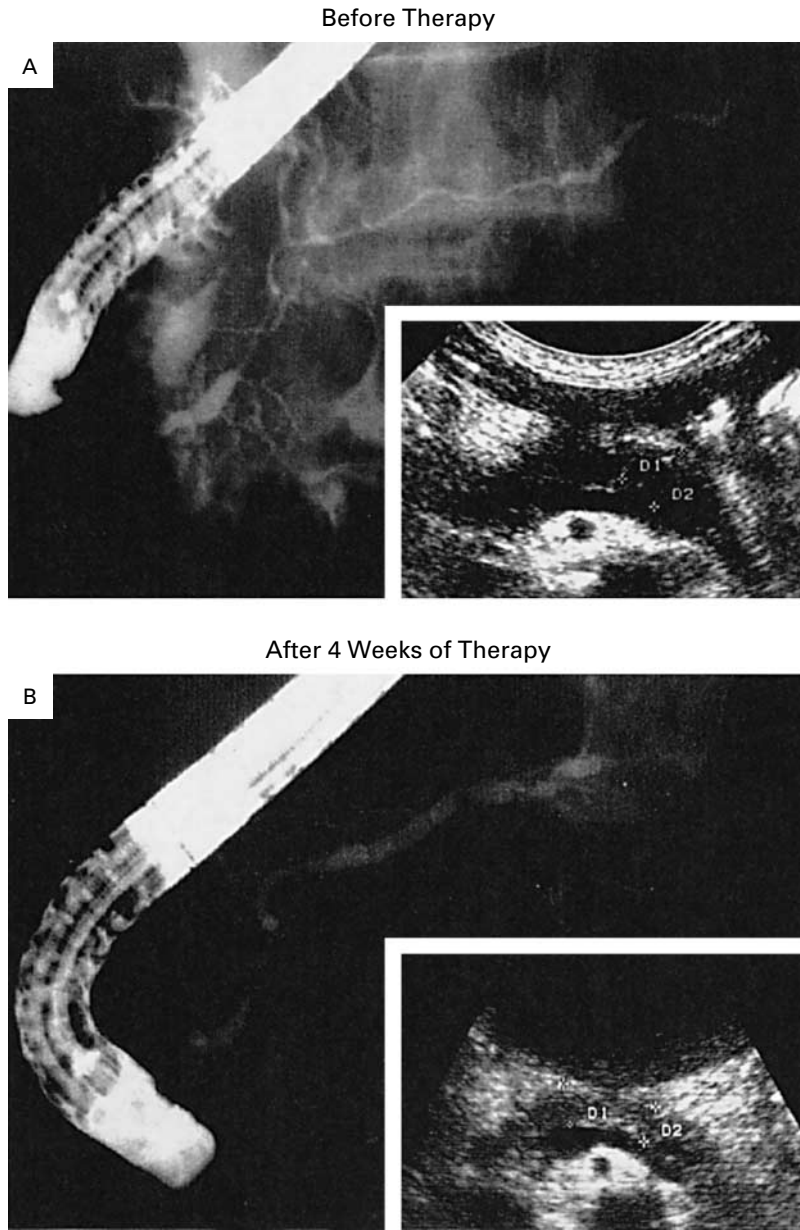
**Figure 1.** Serum IgG4 Concentrations as Determined by Single Radial Immunodiffusion (Panel A) and Serum Total IgG Concentrations (Panel B) in 70 Patients with Pancreatic Cancer, 45 Patients with Ordinary Chronic Pancreatitis, 20 Patients with Sclerosing Pancreatitis, 20 Patients with Primary Biliary Cirrhosis, 8 Patients with Primary Sclerosing Cholangitis, and 11 Patients with Sjögren's Syndrome.

Serum IgG4 and total IgG concentrations above 135 mg per deciliter and 1883 mg per deciliter, respectively (dotted lines), were considered elevated, as determined by an analysis of receiver-operating-characteristic curves.

cells.<sup>18</sup> Patients with pemphigus vulgaris and pemphigus foliaceus, autoimmune skin diseases characterized by the presence of IgG4 autoantibodies against the cell-adhesion molecules desmoglein 3 and desmoglein 1, also have high serum IgG4 concentrations,<sup>27-29</sup> and passive transfer of these IgG4 autoantibodies induces skin disease in animals.<sup>29</sup> In patients with membranous nephropathy, immune complexes containing IgG4 have been detected in serum,<sup>30</sup> and IgG4 is predominantly deposited along the epithelial surface of the glomerular basement membrane.<sup>31</sup>

It is unlikely that the serum concentration of IgG4 increased in our patients with sclerosing pancreatitis as a direct response to exogenous antigen. A parallel increase in the serum IgE concentration was found in only 20 percent of patients, and the median serum IgE concentrations were similar in the patients with sclerosing pancreatitis and the normal subjects.

We found that the patients with sclerosing pancreatitis had elevated serum concentrations of immune complexes and the IgG4 subclass of immune complexes and that these concentrations decreased significantly



**Figure 2.** Findings on Endoscopic Retrograde Cholangiopancreatography and Ultrasonography (Insets) in a 72-Year-Old Woman with Sclerosing Pancreatitis.

Before therapy (Panel A), there is irregular narrowing of the main pancreatic duct and sonolucent swelling of the pancreas. The dimension of the main pancreatic duct (D1) is 1.2 mm, and the dimension of the pancreatic body (D2) is 14.0 mm. After four weeks of glucocorticoid therapy (Panel B), the abnormalities have resolved. The dimension of the pancreatic head (D1) is 9.7 mm, and the dimension of the pancreatic body (D2) is 8.7 mm.

during glucocorticoid therapy. These findings suggest that the pathogenesis of sclerosing pancreatitis is closely related to the immune complexes. Important clinical findings of immune-complex disease are nephritis and vasculitis. We have not found any renal involvement in patients with sclerosing pancreatitis, but we have not excluded the possibility of vascular damage.

Because IgG4 is unique among the IgG subclasses in its inability to fix C1q complement and its low affinity for target antigens,<sup>30</sup> the characteristic features of sclerosing pancreatitis may be closely associated with the IgG4 subclass of immune complexes. The role of immune complexes containing IgG4 differs from that of immune complexes containing other IgG

**TABLE 2.** SERUM IgG AND IgG4 CONCENTRATIONS, SERUM IgG4:IgG RATIO, AND SERUM CONCENTRATIONS OF IMMUNE COMPLEXES AND IMMUNE COMPLEXES OF THE IgG4 SUBCLASS IN 12 PATIENTS WITH SCLEROSING PANCREATITIS BEFORE AND AFTER FOUR WEEKS OF GLUCOCORTICOID THERAPY.

VARIABLE	BEFORE THERAPY		AFTER 4 Wk OF THERAPY		P VALUE*
	median (5th, 95th percentiles)				
Serum IgG (mg/dl)	2389	(1349, 4310)	1138	(604, 1573)	0.002
Serum IgG4 (mg/dl)	742	(265, 1150)	223	(37, 433)	0.002
Serum IgG4:IgG ratio	0.28	(0.18, 0.50)	0.18	(0.03, 0.34)	0.02
Serum immune complexes ( $\mu$ g/ml)	30	(2, 58)	3	(2, 10)	0.003
Serum IgG4 subclass of immune complexes (optical-density units)	1.0	(0.1, 1.7)	0.2	(0.1, 0.5)	0.002

\*The Wilcoxon matched-pairs signed-rank test was used to calculate two-sided P values.

subclasses. In the pathogenesis of membranous nephropathy, for example, these characteristics of IgG4 may account for the slow rate of clearance of this subclass of immune complex from the circulation and for the formation of membrane-attack complexes in tissues as a result of the fixing of complement by means of the alternative pathway.<sup>32</sup>

In conclusion, we found that patients with sclerosing pancreatitis have high serum IgG4 concentrations and that the values are closely associated with disease activity.

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