High Prevalence of Hypothyroidism in Patients with Autoimmune Pancreatitis

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Short title: Hypothyroidism with autoimmune pancreatitis

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Abstract

Purpose: Autoimmune pancreatitis is a unique form of chronic pancreatitis and has been correlated with various extra-pancreatic lesions. To search for a correlation between autoimmune pancreatitis and thyroid lesions, we measured thyroid functions in 41 patients with autoimmune pancreatitis and in 41 patients with chronic calcifying pancreatitis, and investigated the correlation between HLA antigens and hypothyroidism. **Results**: We found a significant difference in the prevalence of anti-thyroglobulin antibody and hypothyroidism between patients with autoimmune pancreatitis and those with chronic pancreatitis (34.1% vs. 7.3%, p=0.005, and 26.8% vs. 0%, p=0.0005, respectively). Patients with hypothyroidism had a significantly higher frequency of anti-thyroglobulin antibody (63.6%) than those without hypothyroidism, but showed no differences in other findings, including serum IgG4 concentration. We could find no significant association between any HLA antigens and the hypothyroid state of autoimmune pancreatitis. **Conclusions**: One quarter of the patients with autoimmune pancreatitis have hypothyroidism that may be independent of the active state of the pancreatic lesion or systemic fibrosing disorder, and thus patients with suspected of having autoimmune pancreatitis should be evaluated for possible hypothyroidism.

Keywords

Autoimmune pancreatitis, Hypothyroidism, IgG4, HLA

Introduction

Recently, a unique form of chronic pancreatitis, autoimmune pancreatitis or lymphoplasmacytic sclerosing pancreatitis (LPSP), has been reported as a discrete disease entity.[1-11] Autoimmune pancreatitis is characterized by irregular narrowing of the main pancreatic duct and sonolucent swelling of the pancreas, both of which are due to abundant lymphoplasmacytic inflammation. In addition, the presence of various autoantibodies and the favorable response to corticosteroid therapy support the notion that an autoimmune mechanism plays a role in its pathogenesis. This disease also shows characteristic features of high serum IgG4 concentrations that reflect disease activity,[12] and

close association with the HLA DRB1*0405-DQB1*0401 haplotype, which may encode specific peptides that in turn initiate the autoimmune process.[13] These findings demonstrate that autoimmune pancreatitis has a distinctive disease profile that clearly distinguishes it from ordinary chronic pancreatitis.

This disease is also characterized by such extra-pancreatic effects as lacrimal and salivary gland lesions,[14] sclerosing cholangitis[8, 9] and retroperitoneal fibrosis.[15,16] The extent of extra-pancreatic lesions and similar pathological findings suggest that this disease is a manifestation of the systemic fibrosing disease, multifocal idiopathic fibrosclerosis.[17]

Comings reported a case of systemic fibrosis that included retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and orbital pseudo-tumor as a multifocal fibrosclerosis.[17] Later, Clark reported that inflammatory change also occurred in the pancreatic tissue.[18] If autoimmune pancreatitis can be classified under the rubric of this systemic fibrosing disease, then we can better understand the reason for its diverse systemic effects.

During follow-up of the patients with autoimmune pancreatitis, we found a few patients who were in need of thyroid hormone supplements because of severe hypothyroidism. Because autoimmune pancreatitis may be a manifestation of multifocal fibrosclerosis, and thyroid lesions are characteristic of multifocal fibrosclerosis, autoimmune pancreatitis may have played a role in the presence of thyroid lesions in these patients. The aim of the present study was to determine whether autoimmune pancreatitis is associated with thyroid impairments by comparing the thyroid state of patients with this disease and patients with ordinary chronic pancreatitis.

Methods

Study Subjects

Between 1994 and 2002, we obtained samples from 41 patients with autoimmune pancreatitis. This group consisted of 32 men and 9 women aged 38 to 86 years (mean age, 62.9±8.9 (SD) years). We also obtained samples from 41 patients with chronic calcifying pancreatitis (25 alcoholic, 16 idiopathic), including 34 men and 7 women aged 41 to 86 years (mean age, 63.7±11.9 years), during the same period.

Autoimmune pancreatitis was defined as in an earlier report,[2,4] namely, as an irregular narrowing of the main pancreatic duct and swelling of the pancreas. In addition to these characteristic findings, we found high serum IgG and IgG4 concentrations (median: 2,131 mg/dl and 550 mg/dl, respectively) in the study group patients and confirmed the characteristic histological findings of lymphoplasmacytic sclerosing pancreatitis (LPSP) (14/41). Patients who showed obstructive jaundice and diffuse pancreatic swelling were treated with 40 mg prednisolone daily for 4 weeks, after which we reduced the dose by 5 mg per week over 7 weeks until a daily dose of 5 mg was reached, which resulted in the improvement of clinical findings. With the exception of chronic thyroiditis, we could find no obvious autoimmune conditions, such as systemic lupus erythematosus, Sjoegren's syndrome, primary biliary cirrhosis, or primary sclerosing cholangitis, in the patients of the study group.

All patients with chronic pancreatitis had marked calcification of the pancreas and marked irregular dilatation of the main pancreatic duct, features not found in patients with autoimmune pancreatitis.

All participants provided written informed consent for invasive tests such as endoscopic retrograde cholangio-pancreatography (ERCP), and prior to the taking of serum samples. The institutional ethics committee granted permission for the HLA study using DNA materials.

Laboratory tests

We measured the serum levels of free T3 (2.5-4.2 ng/L), free T4 (1.0-2.0 ng/dL), thyroid stimulating hormone (TSH) (0.2-4.0 mIU/L), anti-thyroglobulin (anti-Tg) antibody (Tg-Ab kit; Eiken, Tokyo) (<0.7 IU/ML), and anti-thyroid peroxidase (anti-TPO) antibody (TPOAb kit; Cosmic, Tokyo) (<0.1 IU/ML). We obtained serum samples from patients who were in a stable state, because the free T3 level is considered to be affected by acute inflammation of autoimmune pancreatitis or acute attacks of chronic pancreatitis, resulting in low T3 syndrome.

We defined hypothyroidism as a high TSH state, and separated the subjects into two groups according to the following conditions: 1) clinical hypothyroidism with low free T4; and 2) subclinical hypothyroidism with normal free T4.

In addition to ordinary blood tests, including an assay for antinuclear antibody (ANA), we measured the serum concentration of IgG4 (single radial immunodiffusion kit; the Binding Site

Limited, Birmingham, UK) and circulating immune complexes (CIC) (Immune complex mRF "Nissui," Nissui Pharmaceutical Co., Ltd., Tokyo, Japan).

HLA Typing

Among the 41 patients with autoimmune pancreatitis, we performed HLA typing in 37 patients who had agreed to tests involving DNA samples. HLA types at low-resolution level for the HLA-A, -B, -C, -DR, and -DQ loci were determined by means of the polymerase chain reaction (PCR)-sequence-specific primers (SSP) method using a MicroSSP Japanese HLA DNA Typing Tray, Lot #002 (One Lamda, Ganoga Park, CA[]) according to the manufacturer's instructions. High resolution typing of alleles at HLA-DRB1 and -DQB1 was performed by the PCR restriction fragment-length polymorphisms (RFLP) method. HLA class I and class II allelic genotypes from 100 normal subjects, which were obtained in a previous study,[19] were used as a control. Normal subjects were unrelated healthy aphaeresis blood donors living in the central region of Japan.

Statistical analysis

Statistical analysis of the differences in clinical characteristics between patients with autoimmune pancreatitis and those with ordinary chronic pancreatitis was performed by Fisher's exact test or the Mann-Whitney test. Phenotype frequencies were estimated by direct counting of each HLA allele. The significance of an association was evaluated both by Chi-square and Fisher's exact tests. The strength of association was estimated by calculating the odds ratio.

All reported P values are 2-sided. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Thyroid state of patients with autoimmune pancreatitis

We found no significant difference in age or the male:female ratio between patients with autoimmune pancreatitis and those with chronic calcifying pancreatitis ($p=0.69$ and 0.78, respectively) (Table 1).

The frequency of positivity for anti-Tg antibody was significantly greater in patients with autoimmune pancreatitis than in those with chronic pancreatitis (34.1% vs. 7.3%, $p=0.005$). However,

we found no significant difference in the frequency of anti-TPO antibody between the two conditions (17.1% vs. 4.9%, p=0.16) (Table 1).

Five of the patients had severe hypothyroidism and had been treated with thyroid hormone supplements. Among them, 1 patient had been prescribed thyroid hormone prior to the diagnosis of autoimmune pancreatitis, and 4 patients showed hypothyroidism after the occurrence of disease. Another patient had clinical hypothyroidism with a low free T4 level and high TSH level, but received no hormone therapy. Five patients had subclinical hypothyroidism with a normal free T4 level and high TSH level. Although there were 3 patients with ordinary pancreatitis and low free T4, normal free T3, and normal TSH levels, none of the patients with ordinary chronic pancreatitis showed hypothyroidism (i.e., high TSH). Accordingly, we found a significant difference in the frequency of hypothyroidism (i.e., high TSH) between patients with autoimmune pancreatitis and those with chronic pancreatitis (26.8% vs. 0%, p=0.0005) (Table 1).

We found a low free T3 level with normal free T4 and TSH levels (low T3 syndrome) in 9 patients (22.0%) with autoimmune pancreatitis and in 8 patients (19.5%) with ordinary chronic pancreatitis, and found no significant difference between the 2 groups.

Clinical characteristics of patients with hypothyroidism and autoimmune pancreatitis

No patients with hypothyroidism showed significant goiter or severe fibrosis of the thyroid gland invading surrounding organs by physical examination or ultrasonography. In general, the hypothyroidism of these patients was well controlled. We found no significant difference in clinical characteristics—including IgG, IgG4, and CIC values—between patients with hypothyroidism and euthyroid subjects. Patients with hypothyroidism showed a significantly higher frequency of anti-Tg antibody (63.6%) than euthyroid subjects (20.0%). However, we found no significant difference in the frequency of ant-TPO antibody or ANA antibody between the two groups (Table 2).

HLA analysis in patients with autoimmune pancreatitis (AIP) and hypothyroidism

We compared HLA antigen levels among 10 AIP patients with hypothyroidism, 27 euthyroid AIP patients, and 100 normal subjects. We could find no HLA class I or II antigens for which the levels were significantly greater in hypothyroid AIP subjects than in euthyroid AIP or normal subjects,

including A2, DR11, DR15, and DR53, which have been reported to be closely associated with Hashimoto's thyroiditis both in Japan and Western countries (Table 3).[20,21]

Discussion

Positivity for anti-Tg antibody was significantly more frequent in patients with autoimmune pancreatitis than in those with ordinary chronic pancreatitis, but there was no significant difference in the frequency of anti-TPO antibody between the two groups. It has been reported that the prevalence of autoantibodies for thyroid antigens is as high as 30% in patients with other autoimmune diseases, such as Sjoegren's syndrome[22] and systemic lupus erythematosis.[23] Similar to patients with these systemic autoimmune diseases, patients with autoimmune pancreatitis have a tendency to produce autoantibodies for thyroid antigens. In contrast to Hashimoto's thyroiditis, the prevalence of anti-Tg antibody is higher than that of anti-TPO antibody in this condition.[24]

We found a high prevalence of hypothyroidism in patients with autoimmune pancreatitis (26.8%). In fact, the prevalence of hypothyroidism was equivalent to or higher than those of other autoimmune diseases, such as Sjoegren's syndrome,[22] primary biliary cirrhosis,[25] and primary sclerosing cholangitis.[26] We found few patients with disease specific autoantibodies, such as anti-DNA antibody, antimitochondrial antibody and anti-SS-B antibody, and could not detect these autoimmune conditions in our patients, suggesting that the high rate of hypothyroidism was not due to the presence of other autoimmune conditions. A recent study reported that 2 of 11 (18%) patients with lymphoplasmacytic sclerosing pancreatitis (LPSP) showed hypothyroidism among 422 patients with Whipple resection.[27] In patients with autoimmune pancreatitis, hypothyroidism is linked to a high prevalence of anti-Tg antibody. We have no evidence that these autoantibodies directly induce tissue injury. The production of these antibodies may result from antigen presentation secondary to thyroid tissue injury, as reported in patients with thyroid carcinoma.[28] Interaction between activated T cells and the common antigens that are present in both thyroid and pancreatic tissues may induce an immunological response, resulting in tissue injuries in both organs. Though cell surface antigens common to both islet beta cells

and thyroid follicular cells have been reported in patients with non-insulin dependent diabetes mellitus and chronic thyroiditis,[29] we found no common antigens between pancreatic exocrine tissues and thyroid tissues in the present study. Although we could not reveal the exact mechanism for hypothyroidism found in the patient with autoimmune pancreatitis, patients with suspected of having autoimmune pancreatitis should be evaluated for possible hypothyroidism.

A close association between HLA antigens, including A2, DR11, DR15, and DR53, and Hashimoto's disease has been reported for the Japanese population and for Western populations.[20, 21] However, the present study showed no significant association between any HLA antigens and the hypothyroid state of autoimmune pancreatitis, which suggests that the occurrence of hypothyroid state is directly correlated with autoimmune pancreatitis and not with an additional genetic background linked to the occurrence of Hashimoto's thyroiditis. In addition, AIP patients with hypothyroidism showed features atypical of Hashimoto's thyroiditis—i.e., they were preponderantly elderly males, they had no goiter, and they showed a lower prevalence of anti-TPO antibody than anti-thyroglobulin antibody. Unknown factors that induce pancreatic lesions may also induce thyroid impairments, although the present cohort was too small to definitively exclude a contribution by specific HLA antigens. A genome-wide study of regions other than the HLA region may disclose a gene related to conferring susceptibility to hypothyroidism in patients with autoimmune pancreatitis.

We could not confirm that the same pathological process found in pancreatic lesions proceeded in the thyroid lesions, whereas Riedl's thyroiditis has been shown to be the cause of thyroid lesions in patients with multifocal fibrosclerosis.[17, 18] It is possible that different pathological processes proceeded in the two tissue types for the following reasons. First, if the same pathological process exists in thyroid tissue, we would expect to find swelling of the thyroid or the presence of goiter, or the severe fibrosis found in Riedel's thyroiditis, but we did not find significant goiter or severe fibrosis invading the surrounding organs in our patients with autoimmune pancreatitis. Secondly, we could find no significant difference of serum IgG4 value between patients with hypothyroidism and euthyroid patients, which suggests that the hypothyroid state is not associated with the highly active state of this disease found in pancreatic lesions.[12] Finally, steroid therapy could not ameliorate the hypothyroid state (data not shown). The present findings thus indicate that as-yet-unknown

mechanisms operate in the pathogenesis of thyroid lesions associated with autoimmune pancreatitis.

In conclusion, a quarter of the patients with autoimmune pancreatitis in the present study have hypothyroidism with elevated anti-Tg antibody, which may be independent of the active state of the pancreatic lesion or systemic fibrosing disorder, and thus patients with suspected of having autoimmune pancreatitis should be evaluated for possible hypothyroidism.

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Table 1. Comparison of thyroid state between autoimmune pancreatitis and chronic calcifying pancreatitis

	Autoimmune Pancreatitis (n=41)	Calcifying pancreatitis (n=41)	p value
Age	**65.0 (38-76)**	**63.0 (41-86)**	**0.69**
Sex (M/F)	**32 / 9**	**34 / 7**	**0.78**
Anti-Tg or Anti-TPO	**15 (36.6%)**	**5 (12.2%)**	**0.019**
Anti-Tg	**14 (34.1%)**	**3 (7.3%)**	**0.005**
Anti-TPO	**7 (17.1%)**	**2 (4.9%)**	**0.16**
Hypothyroidism: TSH>4 mIU/L	**11 (26.8%)**	**0 (0%)**	**0.0005**
Clinical: FT4<1 ng/dL	**6 (14.6%)**	**0 (0%)**	**0.026**
Subclinical: normal FT4	**5 (12.2%)**	**0 (0%)**	**0.055**
FT4<1 ng/dL and normal FT3, TSH	**7 (17.1%)**	**3 (7.3%)**	**0.32**
FT3<2.5 ng/L and normal FT4, TSH	**9 (22.0%)**	**8 (19.5%)**	**0.79**

Anti-Tg: anti-thyroglobulin antibody; Anti-TPO: anti-thyroid peroxidase antibody;

FT4: free T4; FT3: free T3

Table 2. Differences of clinical characteristics of patients with autoimmune pancreatitis between hypothyroid and euthyroid state.

Clinical Characteristics	Hypothyroid (n=11)	Euthyroid (n=30)	p value
Age	69.0 (50-76)	63.0 (38-76)	0.14
Sex (M/F)	9 / 2	23 / 7	1
IgG (mg/dL)	2269.0 (892-3861)	2114.5 (1029-4562)	0.52
IgG4 (mg/dL)	635.0 (22-1705)	493.0 (8-2855)	0.44
CIC (μ g/ml)	9.9 (2-58.4)	6.7 (2-53.0)	0.91
Autoantibody	7 (63.6%)	8 (26.7%)	0.064
Anti-Tg	7 (63.6%)	6 (20.0%)	0.019
Anti-TPO	4 (36.4%)	3 (10.0%)	0.069
ANA (>x80)	5 (45.5%)	12 (40.0%)	0.7534

Table 3. HLA analysis of AIP patients with hypothyroidism]

HLA analysis	Hypothyroid with AIP n=10	vs. Euthyroid with AIP n=27	p value	vs. Normal subjects n=100	p value
A2	6 (50.0%)	9 (33.3%)	0.142	41 (41%)	0.247
DR11	0 (0%)	1 (3.7%)	0.537	6 (6%)	0.426
DR15	5 (50.0%)	8 (29.6%)	0.249	27 (27%)	0.127
DR53	7 (70.0%)	19 (70.3%)	0.982	56 (56%)	0.393