Pancreatology 14 (2014) 373–379

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Relationship between autoimmune pancreatitis and pancreatic cancer: A single-center experience

Tsukasa Ikeura*, Hideaki Miyoshi, Kazushige Uchida, Toshiro Fukui, Masaaki Shimatani, Yuri Fukui, Kimi Sumimoto, Mitsunobu Matsushita, Makoto Takaoka, Kazuichi Okazaki

The Third Department of Internal Medicine, Kansai Medical University, Osaka, Japan

ARTICLE INFO

Article history:
Available online 21 April 2014

Keywords:
Autoimmune pancreatitis
Pancreatic cancer
Chronic pancreatitis
Carcinogenesis
Diagnosis
IgG4

ABSTRACT

Objectives: Ordinary chronic pancreatitis (CP), such as alcoholic CP, is well established to have the increased risk for pancreatic cancer (PaC), nevertheless an association between autoimmune pancreatitis (AIP) and PaC is still unknown. The aims of this study are to examine the frequency of patients who developed PaC during follow-up after being diagnosed with type 1 AIP and to compare the incidence rate of PaC between patients with type 1 AIP and CP.

Methods: Sixty-three patients with type 1 AIP and 41 patients with CP were enrolled. We examined development of PaC during follow-up from their clinical records.

Results: The mean follow-up period was 62.4 months in AIP group and 49.2 months in CP group. The occurrence of PaC was observed in 3 patients with AIP during the mean follow-up period of 94.7 months (range, 31–186), whereas a single CP patient developed PaC 38 months after CP diagnosis. The incident rate of PaC during follow-up was comparable between the 2 groups [4.8% (3/63) in type 1 AIP group vs. 2.4% (1/41) in CP group]. In all of 3 AIP patients who developed accompanying PaC, the clinical remission of AIP was achieved with maintenance steroid therapy, when tumors were discovered. In the histological examination of one surgical patient with PaC, lymphoplasmacytic infiltration in storiform fibrosis with abundant IgG4-positive cell infiltration was observed around the PaC area.

Conclusions: Similar to patients with ordinary CP, surveillance for development of PaC is needed at regular interval during follow-up in AIP patients.

1. Introduction

Autoimmune pancreatitis (AIP), which was first proposed as a clinical entity by Yoshida et al. in 1995, is characterized by focal or diffuse pancreatic enlargement, irregular narrowing of the main pancreatic duct (MPD), and a dramatic response to steroid therapy [1–4]. To date, 2 AIP subtypes have been recognized, type 1 and type 2[5] The histological features of type 1 AIP include periductal infiltration of lymphocytes, abundant IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis, specifically lymphoplasmacytic sclerosing pancreatitis (LPSP). Type 2 AIP, on the other hand, is histologically characterized by the presence of granulocytic epithelial lesions without IgG4-positive plasma cell infiltration, specifically idiopathic duct-centric chronic pancreatitis (IDCP) or AIP with granulocyte epithelial lesions (GELs) [6,7]. Previous studies have reported the distinguishing characteristics in clinical profiles and outcomes of type 1 and type 2 AIP [8–12]. Type 1 AIP is classified as a pancreatic manifestation of IgG4-related disease, and is probably a systemic disease with an abnormal immunological process [13].

Currently, little is known about the natural clinical history of AIP. The prognosis of AIP is considered to be favorable because it is responsive to steroid therapy. However, reports indicate that 24–57% of the patients who receive steroid therapy experience a relapse [13–15]. Additionally, previous papers have suggested an association between AIP and pancreatic cancer (PaC) [16–24]. It is extremely important for clinicians to recognize the validity and the magnitude of the association between AIP and PaC, although whether patients suffering from AIP are more susceptible to PaC has not been clearly elucidated.

The aims of this study were to examine the frequency with which patients developed PaC during follow-up after being

* Corresponding author. The Third Department of Internal Medicine, Kansai Medical University, 2-3-1, Shinmachi, Hirakata, 573-1191 Osaka, Japan. Tel.: +81 72 804 0101; fax: +81 72 804 2524.
E-mail address: ikeurat@takii.kmu.ac.jp (T. Ikeura).

http://dx.doi.org/10.1016/j.pan.2014.04.029

diagnosed with type 1 AIP, to clarify the clinical and histological characteristics of type 1 AIP patients with PaC, and to compare the incidence rate of PaC between patients with type 1 AIP and ordinary chronic pancreatitis (CP), which is a well-established risk factor for PaC [25,26].

2. Methods

2.1. Identification of type 1 AIP patients

We reviewed data from all AIP patients included in our database starting in 2002. We applied the international consensus diagnostic criteria (ICDC) to each patient based on clinical, serological, radiological, and histological findings [5]. The current study included patients diagnosed with type 1 AIP who were followed for more than 1 year using imaging modalities. These criteria led to inclusion of 63 patients suffering from type 1 AIP (definitive type 1 AIP in 61 patients, and probable type 1 AIP in 2 patients) in the study. Many of these patients were included in the previously published papers [22,27,28].

For the purpose of this study, we used clinical records to retrieve patient data, including age at the clinical onset of the disease, sex, length of observation period, and development of PaC or extrapancreatic cancer during the follow-up period. The observation period was defined as the time from the diagnosis of AIP until the final contact or, in cases accompanied by PaC, until the diagnosis of PaC. To allow further analysis of the clinical factors associated with development of PaC in type 1 AIP patients, we also collected the following information: alcohol and smoking habits, medical history, diabetes history, pancreatic parenchymal finding, pancreatic ductal finding, IgG4 serum levels, other organ involvement, therapy for the disease (steroid, resection, no treatment), and disease relapse.

2.2. Identification of ordinary CP patients

Clinical information of ordinary CP patients, including alcoholic CP and hereditary CP patients, who were observed at our institution from November 2002 to December 2011, were retrospectively reviewed to compare the incidence rate of PaC between patients with type 1 AIP and patients with ordinary CP. Of these CP patients, only CP patients who were followed for more than 1 year using imaging modalities were included in the current study. The diagnosis of CP was based on the clinical diagnostic criteria proposed by the Japan Pancreas Society [29]. We enrolled 41 CP patients (34 with definitive CP and 7 with probable CP). Briefly, 34 patients diagnosed as definitive CP had multiple calcifications distributed in the entire pancreas on computed tomography (CT), and 7 patients diagnosed as probable CP had no calcification in the pancreas but irregular dilatation of the MPD throughout the entire pancreas plus pancreatic deformity with irregular contour on CT. As with type 1 AIP patients, clinical information of included CP patients was reviewed.

2.3. Definitions

Patients were divided into 2 groups based on their alcohol consumption: (1) teetotalers (non-drinkers), and (2) drinkers. They were also divided on the basis of smoking habits into non-smokers and smokers.

Diabetes was defined as a fasting glucose level >126 mg/dL or a glucose level >201 mg/dL 2 h after an oral glucose tolerance test.

The upper limit of normal value of serum IgG4 was defined as 135 mg/dL [30].

Initial steroid therapy was performed with either conventional oral steroid therapy or steroid pulse therapy [31,32]. For conventional oral steroid therapy, prednisolone was administrated at an initial dose of 30–40 mg per day for 2 weeks, and was subsequently gradually tapered by 5 mg every 1–2 weeks until the maintenance dosage was reached. Steroid pulse therapy involved intravenous administration of methylprednisolone at a dose of 500 mg per day for 3 consecutive days per week for 2 straight weeks. After steroid pulse therapy, we administered prednisolone at 20 mg per day, and it was gradually tapered until the maintenance dosage was reached. After initial steroid therapy, if needed, maintenance steroid therapy was performed for at least 6 months with prednisolone at a dose of 2.5–5.0 mg per day to prevent relapse.

AIP relapse was defined as the reappearance of pancreatic or extrapancreatic involvement after steroid withdrawal.

2.4. Statistical analysis

Differences among the groups were analyzed using chi-squared test or Fisher's Exact test for qualitative variables, and Mann–Whitney's *U* test for quantitative variables. A p-value >0.05 was considered statistically significant.

3. Results

3.1. Characteristics of type 1 AIP patients

The characteristics of the 63 patients with type 1 AIP are shown in Table 1. The mean follow-up period was 62.4 months (range, 12–195 months). All patients underwent imaging modalities, such as

Table 1
Characteristics of patients with type 1 AIP.

	All patients ($N = 63$)
Male sex	45 (71%)
Mean age at AIP diagnosis, y	62.6 (19–80)
Mean observation period, mo	62.4 (12–195)
Drinkers	5 (8%)
Smokers	26 (41%)
Diabetes	22 (35%)
Enlargement of pancreas	
Diffuse	26 (41%)
Focal	30 (48%)
None	7 (11%)
Narrowing of MPD	
Long or multiple	30/57 (53%)
Focal	22/57 (39%)
None	5/57 (8%)
Elevated serum IgG4	
>2× upper limit of normal value	40/61 (66%)
1–2× upper limit of normal value	17/61 (28%)
None	4/61 (6%)
OOI	
Sclerosing cholangitis	9 (14%)
Enlarged salivary/lachrymal glands	7 (11%)
Retroperitoneal fibrosis	5 (8%)
Renal involvement	3 (5%)
Initial therapy	
Steroid	51 (81%)
Resection	7 (11%)
Conservative follow-up	5 (8%)
Maintenance steroid therapy	39/51 (76%)
Relapse	12 (19%)
Development of malignancies	
Pancreatic cancer	3 (5%)
Gastric cancer	2 (3%)
Colon cancer	1 (2%)
Leukemia	1 (2%)
Melanoma	1 (2%)