Differentiation of Autoimmune Pancreatitis From Pancreatic Cancer by Diffusion-Weighted MRI

Terumi Kamisawa, MD[1], Kensuke Takuma, MD[1], Hajime Anjiki, MD[1], Naoto Egawa, MD[1], Tastuo Hata, MD[2], Masanao Kurata, MD[2], Goro Honda, MD[2], Kouji Tsuruta, MD[2], Mizuka Suzuki, MD[3], Noriko Kamata, MD[3] and Tsuneo Sasaki, MD[4]

OBJECTIVES: **We sought to clarify the clinical utility of diffusion-weighted magnetic resonance imaging (DWI) for differentiating autoimmune pancreatitis (AIP) from pancreatic cancer.**

METHODS: **Thirteen AIP patients underwent DWI before therapy, and six of them underwent DWI after steroid therapy. The extent and shape of high-intensity areas were compared with those of 40 pancreatic cancer patients. Apparent diffusion coefficient (ADC) values were calculated in the AIP area before and after steroid therapy in pancreatic cancer patients and in a normal pancreatic body.**

RESULTS: **On DWI, AIP and pancreatic cancer were detected as high-signal intensity areas. The high-intensity areas were diffuse ($n=4$), solitary ($n=6$), and multiple ($n=3$) in AIP patients, but all pancreatic cancer patients showed solitary areas ($P<0.001$). A nodular shape was significantly more frequent in pancreatic cancer, and a longitudinal shape was more frequently found in AIP ($P=0.005$). ADC values were significantly lower in AIP ($1.012\pm0.112\times10^{-3}$ mm^2/s) than in pancreatic cancer ($1.249\pm0.113\times10^{-3}$ mm^2/s) and normal pancreas ($1.491\pm0.162\times10^{-3}$ mm^2/s) ($P<0.001$). Receiver operating characteristic analysis yielded an optimal ADC cutoff value of 1.075×10^{-3} mm^2/s to distinguish AIP from pancreatic cancer. After steroid therapy, high-intensity areas on DWI disappeared or were markedly decreased, and the ADC values of the reduced pancreatic lesions increased almost to the values of normal pancreas.**

CONCLUSIONS: **DWI is useful for detecting AIP and for evaluating the effect of steroid therapy. ADC values were significantly lower in AIP than in pancreatic cancer. An ADC cutoff value may be useful for distinguishing AIP from pancreatic cancer.**

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a type of pancreatitis with a presumed autoimmune etiology. AIP is characterized radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct, serologically by elevation of serum IgG4 levels, histopathologically by fibrosis with dense infiltration of T lymphocytes and IgG4-positive plasma cells in the peripancreatic and interlobular area of the pancreas, and clinically by a preponderance of elderly men and good responsiveness to steroid therapy (1–4). As AIP patients often present with painless jaundice in the setting of a pancreatic mass, they are sometimes misdiagnosed as having pancreatic cancer and undergo pancreatic resection (5). In North America, about 2.5% of pancreatoduodenectomies were performed for AIP because of a mistaken diagnosis of pancreatic cancer (6). As AIP responds dramatically to steroid therapy, to avoid unnecessary surgery, an accurate differential diagnosis between AIP and pancreatic cancer is required. As it is usually difficult to take adequate biopsy specimens from the pancreas, AIP is currently diagnosed on the basis of a combination of clinical, laboratory, and imaging studies (1–4). Recently, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been used to diagnose pancreatic cancer; however, it cannot definitively differentiate AIP from pancreatic cancer, as inflammatory foci in the pancreas also accumulate FDG (7).

Recent technical developments make diffusion-weighted magnetic resonance imaging (DWI) of the body feasible, and DWI has been increasingly used to evaluate diseases involving abdominal organs. DWI is a technique in which phase-defocusing and -refocusing

[1]Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; [2]Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; [3]Department of Radiology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; [4]Department of Chemotherapy, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan. **Correspondence:** Terumi Kamisawa, MD, Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. E-mail: kamisawa@cick.jp
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gradients are used to evaluate the rate of microscopic water diffusion within tissues (8,9). Quantitative measurements of the diffusivity of water are described by the apparent diffusion coefficient (ADC). ADC represents microcirculation of blood perfusion, as well as molecular diffusion of water. The ability to measure the rate of water diffusion within the tissue is important, as water diffusion is frequently altered in various disease processes and may reflect physiological and morphological characteristics, such as cell density and tissue viability. Decreased ADC values correlate with increased tumor cellularity and the total nuclear area, which restrict water diffusion (10–12). In general, malignant tumors have a higher cellularity than benign lesions; therefore, ADC values assist in differentiating between malignant and benign lesions (10–13). It has been reported that ADC values are lower in pancreatic cancer than in the normal pancreas (14–16). This study aimed at clarifying the clinical utility of DWI for differentiating AIP from pancreatic cancer.

METHODS

This study was approved by our institutional review board, and all subjects gave their written informed consent.

Study subjects

Between January 2008 and December 2009, 13 AIP patients (eight men, five women; mean age±s.d. 58.6±16.4 years; age range 25–83 years) who prospectively underwent DWI were enrolled in this study. The diagnosis of AIP was based on the revised diagnostic criteria for AIP (4) as follows: enlargement of the pancreas (diffuse ($n=5$) or segmental (body and tail ($n=2$), body ($n=3$), and tail ($n=3$))); irregular narrowing of the main pancreatic duct (diffuse ($n=6$) or segmental ($n=7$)); elevation of serum IgG4 ($n=11$); presence of autoantibodies ($n=7$); and histological findings of lymphoplasmacytic sclerosing pancreatitis with abundant infiltration of IgG4-positive plasma cells in endoscopic ultrasonography-guided fine needle aspiration specimens with a 19-gauge needle ($n=3$) and sclerosing sialadenitis with abundant infiltration of IgG4-positive plasma cells in surgically biopsied submandibular glands ($n=4$). Seven patients underwent steroid therapy and responded well. The other six patients with segmental AIP lesions were asymptomatic, and were followed-up conservatively. All patients also fulfilled the HISORt criteria for AIP (17).

The patients underwent DWI before any therapy, and six patients who were treated with steroids underwent DWI again about 2 months after steroid therapy. During the same period, 40 patients (23 men, 17 women; mean age±s.d. 59.8±16.8 years) with pancreatic cancer, histologically confirmed as ductal adenocarcinoma, also underwent DWI. The main locations of pancreatic cancer were the head ($n=10$), body ($n=20$), and tail ($n=10$). Tumor category classified according to the International Union Against Cancer TNM system (18) was T2 ($n=4$), T3 ($n=19$), and T4 ($n=17$). All tumors were radiologically solid without a cystic component. Surgical resection was performed in 10 patients (pylorus preserving pancreatoduodenectomy ($n=5$) and distal pancreatectomy ($n=5$)), and the other patients were treated with chemotherapy or conservatively. The imaging results of the pancreatic body of 30 patients (20 men, 10 women; mean age±s.d. 59.8±14.7 years) with hepatic tumors who underwent DWI were used as normal controls. There were no differences in age and sex ratio between AIP patients and pancreatic cancer patients or normal controls. There were no differences in body mass index between AIP patients (21.5±3.0 kg/m^2) and pancreatic cancer patients (20.9±3.1 kg/m^2) or normal controls (21.2±2.8 kg/m^2).

Magnetic resonance imaging

All magnetic resonance imaging (MRI) examinations were performed on a clinical 1.5-T MRI scanner (MAGNETOM Avant, Siemens Medical Solutions, Erlangen, Germany). All MR images, including T1-weighted images (T1WI), T2-weighted images (T2WI), and DWI, were obtained during the same examination. DWI was obtained using a single-shot echo-planar imaging sequence. For respiratory triggering, prospective acquisition correction was implemented. Technical parameters were as follows: repetition time/echo time = respiratory rate/78 ms, field of view = 380 mm, acquisition matrix = 81×175, slice thickness of 7 mm, intersection gap of 2.3 mm, and water excitation with b values of 0, 50, and 800 mm^2/s. The motion-probing gradient pulses were placed in the X-, Y-, and Z-axes. The total acquisition time for the DWI examination in each patient was ~3.5 min.

As the signal intensity on DWI can be affected by the signal intensity on T2WI, high-intensity tissues on T2WI may exhibit increased signal intensity on DWI with a low b value. In reality, on $b=0$ mm^2/s images, the fat tissue signal is suppressed, and water appears bright, whereas $b=50$ mm^2/s images are often called black-blood images because the loss of signal intensity caused by blood flow renders vessels dark. DWI with a higher b value (800 mm^2/s) may be required to avoid the influence of intensity on T2WI, the so-called T2 shine-through effect. Therefore, all DWI images were acquired with a diffusion factor, b, of 0, 50, or 800 s/mm^2, and ADC maps were reconstructed in all cases.

High-signal intensity areas on DWI were assessed in AIP and pancreatic cancer cases on the basis of the following points: extent of the area; diffuse or segmental (solitary or multiple); and shape of segmental lesions (nodular or longitudinal). The maximum diameter of the largest segmental lesion was measured. The investigator was blinded to the clinical diagnosis.

Calculation of ADC values

All ADC values were calculated on a workstation with standard software (ShadeQuest; Yokogawa Electric, Tokyo, Japan). The ADC values of primary tumors were determined by measuring the region of interest (ROI) created on each ADC map. ADC maps were constructed from images with three different b factors (0, 50, and 800 mm^2/s). Three different circular ROIs were drawn on the images of the ADC map at the slice with the greatest area of lesions by two separate technologists (19). The most representative image was used. Care was taken to avoid pancreatic ducts, cystic lesions, and artifacts within the ROIs. The mean value of a total of six different ADCs was defined as the ADC value. In patients with multifocal-type AIP, ADC values were measured in the largest lesion.

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Statistical analysis

All data are expressed as means ± s.d. The Mann–Whitney *U*-test was used to compare the differences in ADC values. To determine the ADC values that could be used to distinguish AIP from pancreatic cancer, receiver operator characteristic (ROC) curves were used. All *P* values were two-sided, and the significance level was 0.05. All statistical analyses were performed using Dr SPSSII for Windows (Statistical Package for Social Science, release 11.0.1J, SPSS Japan, Tokyo, Japan). All patients provided their written informed consent for these tests.

RESULTS

On DWI with a high *b* value, nine AIP cases and all pancreatic cancer cases were clearly detected as high-signal intensity areas relative to the surrounding pancreatic tissue; however, the intensity was lower in the other four AIP cases compared with pancreatic cancer. The high-intensity areas were diffuse ($n=4$, **Figure 1a** and **b**), solitary ($n=6$), and multiple ($n=3$) in AIP patients, but all pancreatic cancer patients showed a solitary area ($P<0.001$). With regard to the shape of the high-intensity area, a longitudinal shape was significantly more frequent in AIP (**Figure 2a** and **b**), and a nodular shape was more frequently found in pancreatic cancer (**Figure 3a** and **b**, $P=0.005$). There was no significant difference in the maximum diameter of segmental high-intensity areas between the two diseases (**Table 1**).

The ADC values were $1.012\pm0.112\times10^{-3}$ mm^2/s in AIP, $1.249\pm0.113\times10^{-3}$ mm^2/s in pancreatic cancer, and $1.491\pm0.162\times10^{-3}$ mm^2/s in normal pancreatic tissue. The ADC values were significantly lower in AIP and pancreatic cancer than in normal pancreatic tissue ($P<0.001$). Furthermore, the ADC values were significantly lower in AIP than in pancreatic cancer (**Figure 4**, $P<0.001$).

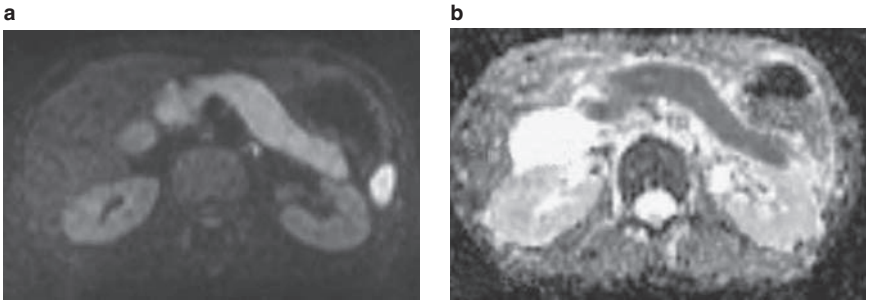

Figure 1. Diffuse-type autoimmune pancreatitis. (**a**) Diffusion-weighted magnetic resonance image showing a diffusely swollen high-intensity area ($b=800$ mm^2/s). (**b**) ADC map in the same patient. ADC, apparent diffusion coefficient.

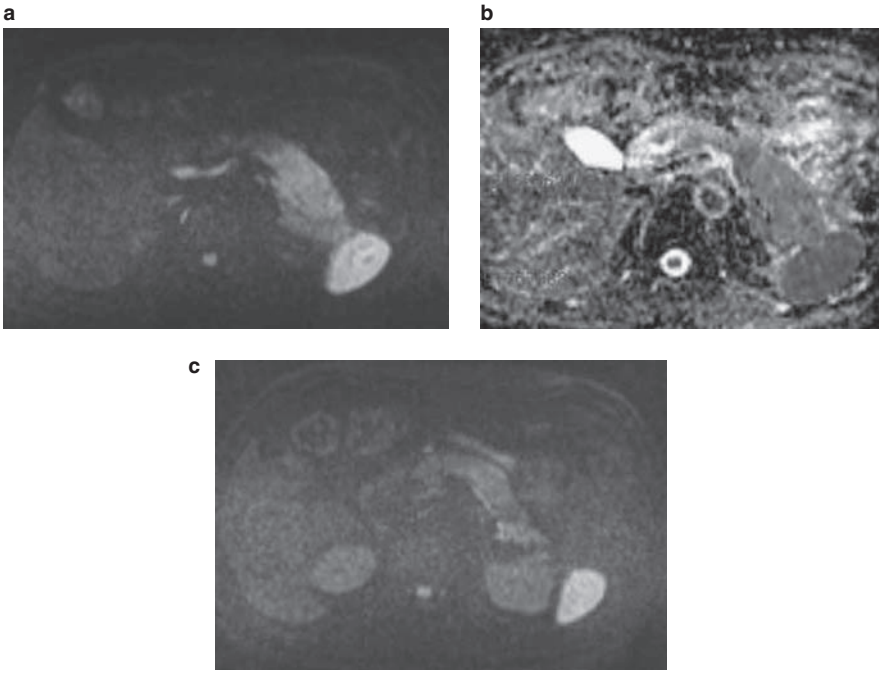

Figure 2. Segmental-type autoimmune pancreatitis. (**a**) Diffusion-weighted magnetic resonance imaging showing a longitudinal high-intensity area ($b=800$ mm^2/s). (**b**) ADC map in the same patient. (**c**) Diffusion-weighted magnetic resonance imaging showing a markedly decreased high-intensity area 2 months after starting steroid therapy ($b=800$ mm^2/s). ADC, apparent diffusion coefficient.

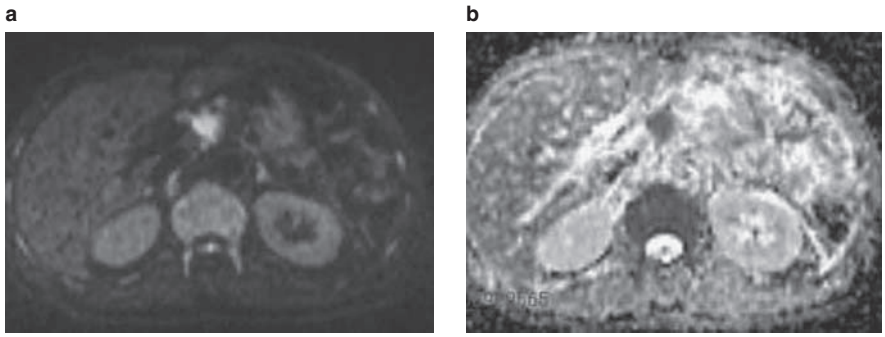

Figure 3. Pancreatic head cancer. (**a**) Diffusion-weighted magnetic resonance imaging showing a nodular high-intensity area (b=800 mm²/s). (**b**) ADC map in the same patient. ADC, apparent diffusion coefficient.

Table 1. High-intensity areas on DWI in AIP and pancreatic cancer

High-intensity area	AIP (n=13)	Pancreatic cancer (n=40)	P value
Extent			
Diffuse	4	0	0.002
Segmental			
Solitary	6	40	<0.001
Multiple	3	0	0.012
Shape			
Nodular	2	30	0.005
Longitudinal	7	10	
Maximum diameter of segmental area (mm)	65.9±31.6[a]	45.4±16.1	0.068

AIP, autoimmune pancreatitis; DWI, diffusion-weighted magnetic resonance imaging.
[a]Data are expressed as mean±s.d.

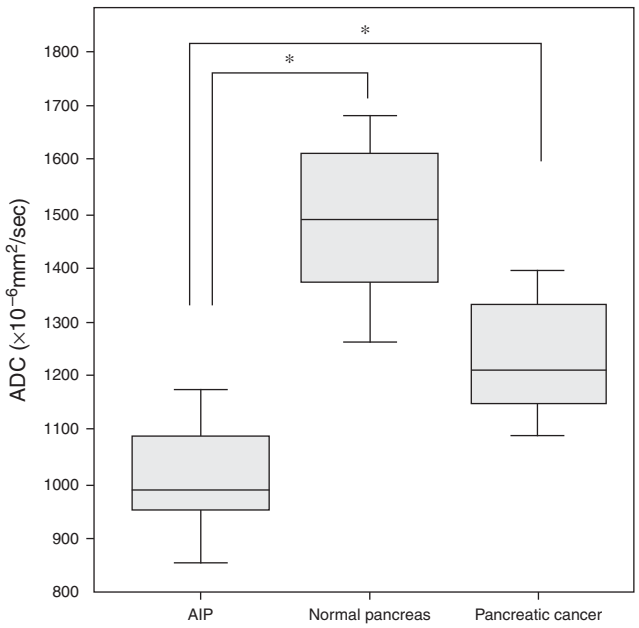

Figure 4. Box plots of ADC values of AIP, normal pancreas, and pancreatic cancer. The ADC values for AIP (1.015±0.122×10⁻³ mm²/s) were significantly lower than those for pancreatic cancer (1.225±0.113×10⁻³ mm²/s) and normal pancreas (1.488±0.185×10⁻³ mm²/s) (*P<0.001). ADC, apparent diffusion coefficient; AIP, autoimmune pancreatitis.

On the basis of the ROC curve data, the optimal ADC cutoff value to distinguish AIP from pancreatic cancer was 1.075×10⁻³ mm²/s. Using this cutoff value, sensitivity was 92.5%, specificity was 76.9%, and the area under the curve was 0.87 (**Figure 5**). ADC values in 37 of 40 pancreatic cancer patients were >1.075×10⁻³ mm²/s, and in 10 of 13 AIP patients they were <1.075×10⁻³ mm²/s (P<0.001). The three AIP patients, whose ADC values (1.218×10⁻³ mm²/s, 1.163×10⁻³ mm²/s, and 1.153×10⁻³ mm²/s) were >1.075×10⁻³ mm²/s, could be differentiated from those with pancreatic cancer by their elevated serum IgG4 levels. There were no significant differences in ADC values between diffuse AIP (1.005±0.112×10⁻³ mm²/s) and solitary AIP (1.037±0.123×10⁻³ mm²/s).

After steroid therapy, the enlarged pancreas decreased to its normal size, and the high-intensity area on DWI disappeared or was markedly decreased in all six AIP patients (**Figure 2c**). The ADC values of the reduced pancreatic lesions increased almost to the values of normal pancreas after steroid therapy (**Figure 6**). Posttreatment ADC values of lesions (1.469±0.194×10⁻³ mm²/s) were significantly higher than pretreatment ADC values (0.967±0.117×10⁻³ mm²/s) (P=0.003).

DISCUSSION

As AIP can mimic pancreatic cancer clinically and radiologically, it is of utmost importance to differentiate between these two diseases. Imaging studies have an important function, as there is no definite serological marker for AIP. Typical AIP cases showing diffuse enlargement of the pancreas with a capsule-like rim on CT or MRI are diagnosed relatively easily. However, segmental AIP cases are sometimes difficult to distinguish from pancreatic cancer cases, even with CT, MRI, and FDG-PET (1–7).

DWI is a method of probing the random motion of water molecules, which depends on their microenvironment. DWI of the brain has been used clinically for more than a decade, and the usefulness of DWI for imaging of various cancers in abdominal organs has been reported (9,11,12,14–16). On DWI, AIP and pancreatic

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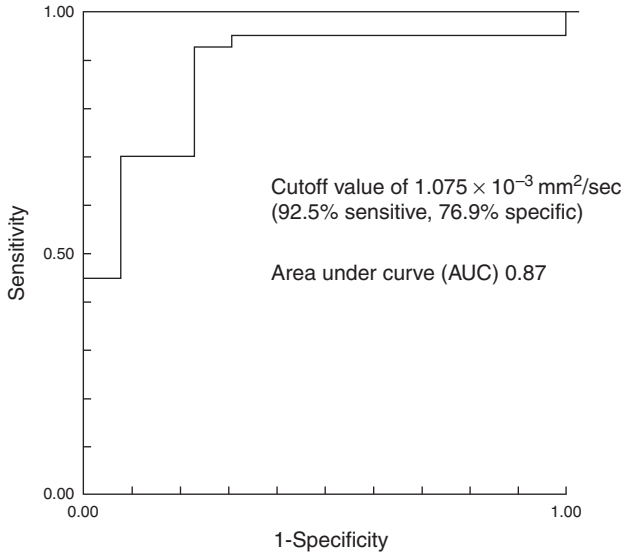

Figure 5. The receiver operating characteristic curve evaluating the optimal ADC cutoff value to distinguish AIP from pancreatic cancer. ADC, apparent diffusion coefficient; AIP, autoimmune pancreatitis.

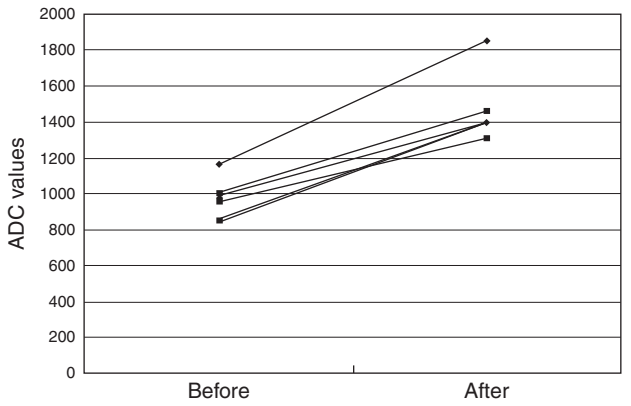

Figure 6. ADC values ($\times 10^{-6}$ mm^2/s) of the pancreas with autoimmune pancreatitis before and after steroid therapy. ADC, apparent diffusion coefficient.

cancer were detected as high-signal intensity areas. However, as all pancreatic cancers showed a solitary area, diffuse or multiple high-intensity areas suggested AIP. A longitudinal high-intensity area also suggested AIP more than pancreatic cancer.

It is reported that pancreatic cancer showed lower ADC values ($1.27\pm0.52\times10^{-3}$ mm^2/s (15) or $1.44\pm0.20\times10^{-3}$ mm^2/s (14)) compared with normal pancreas because of increased cellularity and fibrosis (desmoplasia) of the tumor, which cause restricted diffusion. In this study, the ADC value of pancreatic cancer was $1.249\pm0.113\times10^{-3}$ mm^2/s, which was also significantly lower than that of normal pancreatic tissue. On the other hand, the ADC value of AIP was $1.012\pm0.112\times10^{-3}$ mm^2/s, which was significantly lower than that of pancreatic cancer. There are only two reports of ADC values in AIP. Feuerlein *et al.* (20) reported an ADC value of 0.799×10^{-3} mm^2/s in one patient with diffuse AIP. Taniguchi *et al.* (19) reported that the ADC values of four AIP patients ($0.97\pm0.18\times10^{-3}$ mm^2/s) were significantly lower than those of normal controls. ADC values, which are quantitative expressions of tissue diffusion characteristics, are related to the proportion of extracellular components. Guo *et al.* (21) reported a clear inverse relationship between ADC values and the cellular component of brain tumors, such as lymphoma and high-grade astrocytoma. The ADC value was significantly lower in lymphomas than in high-grade gliomas, whereas the cellular component was significantly greater in lymphomas than in high-grade gliomas. These findings suggest that increased cellularity is associated with more restricted diffusion. Thus, ADC values tend to decrease with increased tissue cellularity or cell density.

The histopathology of the pancreas in AIP is very characteristic: dense infiltration of lymphocytes and plasma cells with dense fibrosis or edema in the involved pancreatic lesion (1–4). Although cancer cell infiltration with desmoplastic stroma is the typical histopathological feature of pancreatic cancer, the cellularity of dense lymphoplasmacytic infiltration in AIP is obviously greater than that of pancreatic cancer. Increased cellularity and edematous change in AIP may induce lower ADC values in AIP than in pancreatic cancer. Using an ADC cutoff value (1.075×10^{-3} mm^2/s) seems to be useful for distinguishing AIP from pancreatic cancer.

After steroid therapy, high-intensity areas on DWI disappeared or were markedly decreased with improvement in pancreatic enlargement. The ADC values of reduced pancreatic lesions increased to nearly that of normal pancreas after steroid therapy. DWI may also be useful for evaluating the effect of steroid therapy and for monitoring relapse during follow-up.

This study had some limitations. The first limitation was the lack of histopathology of the pancreas in 10 AIP patients, so that the degree of lymphoplasmacytic infiltration could not be assessed. The second limitation was the small number of AIP patients examined. Moreover, as AIP is a relatively rare disease, there were only 13 AIP patients. A further study of more cases is necessary. However, this is the first report about the utility of DWI to distinguish AIP from pancreatic cancer; therefore, a prospective, differential diagnostic study on using this cutoff value will further elucidate the utility of DWI.

In conclusion, DWI is useful for detecting AIP and for evaluating the effect of steroid therapy. ADC values were significantly lower in AIP than in pancreatic cancer. An ADC cutoff value may be useful for distinguishing AIP from pancreatic cancer.

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CONFLICT OF INTEREST

Guarantor of the article: Terumi Kamisawa, MD.
Specific author contributions: None.
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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ It is sometimes difficult to differentiate autoimmune pancreatitis (AIP) from pancreatic cancer.

WHAT IS NEW HERE

- ✓ On diffusion-weighted magnetic resonance imaging (DWI), diffuse or multiple high-signal intensity areas suggest autoimmune pancreatitis (AIP) rather than pancreatic cancer.
- ✓ The apparent diffusion coefficient (ADC) values for AIP were significantly lower than those for pancreatic cancer.
- ✓ An ADC cutoff value of 1.075×10^{-3} mm^2/s may be useful for distinguishing AIP from pancreatic cancer.
- ✓ After steroid therapy, the ADC values of the reduced pancreatic lesion increased almost to the values of normal pancreas.

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