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Case Report

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## The usefulness of IgG4 and apparent diffusion coefficient value for the diagnosis of a case of autoimmune pancreatitis

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### Abstract

A 65-year-old man was admitted with aggravated abdominal pain. Ultrasonography revealed an dilated intrahepatic bile duct. Abdominal plain computed tomography showed a sausage-like swelling over the entire pancreas and a dilated biliary tract. Fat-suppressed T1-weighted (T1W) images by magnetic resonance imaging (MRI) showed the overall pancreas to have low signal intensity, with a hypointense band at the edge of the pancreatic body. T2-weighted half-Fourier acquisition single-shot turbo spin-echo images showed narrowing of the main pancreatic duct in the pancreatic body, and similarly to the fat-suppressed T1W images, a hypointense band at the edge of the pancreatic body. MR cholangiopancreatography (MRCP) showed narrowing of the main pancreatic duct in the pancreatic head and body. The intrapancreatic portion of the common bile duct was also narrowed, and significant dilatation was observed from the common bile duct through the intrahepatic bile duct. Diffusion-weighted images showed the overall pancreas to have a mildly high signal intensity, with an apparent diffusion coefficient value of  $1.11 \times 10^{-3} \text{ mm}^2/\text{sec}$ . Because of the high level of soluble interleukin-2 receptor observed, a diffuse enlarged type of primary pancreatic malignant lymphoma was suspected; however, since the IgG4 level was markedly elevated, autoimmune pancreatitis was diagnosed.

Steroid therapy improved the patient's symptoms. Fat-suppressed T1W images showed a smaller pancreas with normalized signal intensity. MRCP showed no narrowing in the main pancreatic duct. In addition, the narrowing of the intrapancreatic portion of the common bile duct resolved, and the dilatation of the biliary tract improved.

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### Introduction

Autoimmune pancreatitis is defined as pancreatitis with findings suggestive of involvement of autoimmune

mechanisms, such as high serum gammaglobulin and/or IgG, or the presence of autoantibodies, with response to steroid therapy<sup>1)</sup>. Morphologically, most cases show diffuse swelling of the pancreas and a narrowed main

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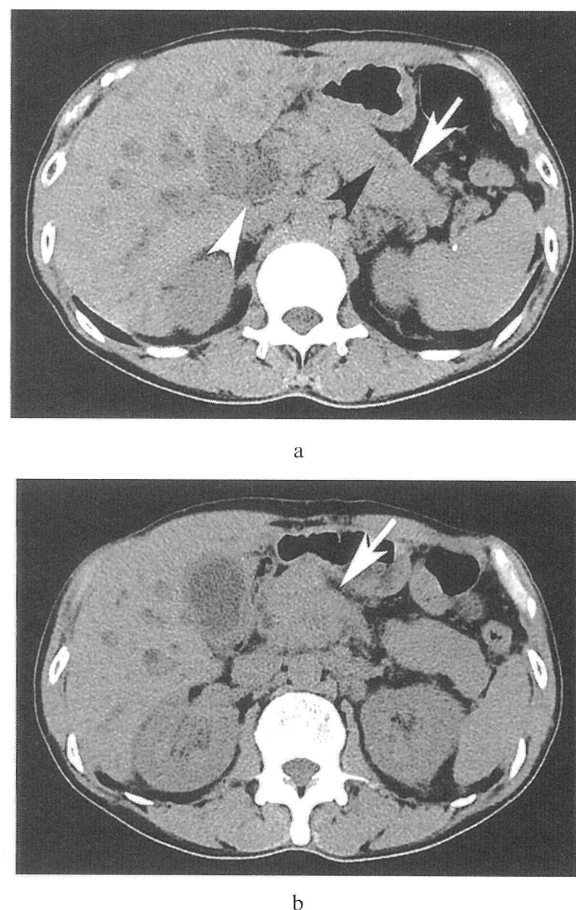
pancreatic duct. Although this disease is widely recognized, as this recognition extends, the number of reports on lesions other than the pancreas, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, is growing. The clinical diagnostic criteria of autoimmune pancreatitis were revised in 2006; the main criteria are narrowing of the main pancreatic duct and swelling of the pancreas, as shown by diagnostic imaging<sup>2)</sup>. On the other hand, the diffuse enlarged type of primary pancreatic malignant lymphoma is rarely found, but the diagnostic images are similar to those of autoimmune pancreatitis. These two diseases have largely different treatments and prognoses and hence should be appropriately distinguished. Here we report a case of autoimmune pancreatitis for which the apparent diffusion coefficient (ADC) value was useful for distinguishing the case from the diffuse enlarged type of primary pancreatic malignant lymphoma.

### Case

A 65-year-old man had experienced abdominal discomfort for 1 month, for which he had been taking various medicines. His abdominal pain became aggravated, and ultrasonography showed a dilated intrahepatic bile duct, so he was admitted. He had a history of bronchial asthma.

Peripheral blood tests at admission revealed elevated white blood cell and platelet counts of  $11,330/\mu\text{L}$  and  $438,000/\mu\text{L}$ , respectively. Blood biochemistry results showed elevated serum protein level of  $11.2\text{ g/dL}$ , AST of  $108\text{ U/L}$ , ALT of  $121\text{ U/L}$ , ALP of  $854\text{ U/L}$ , LAP of  $182\text{ U/L}$ , LD of  $239\text{ U/L}$ , and total bilirubin of  $2.9\text{ mg/dL}$ ; the AMY level was normal. Tumor markers (CEA, CA19-9) were also within the normal range.

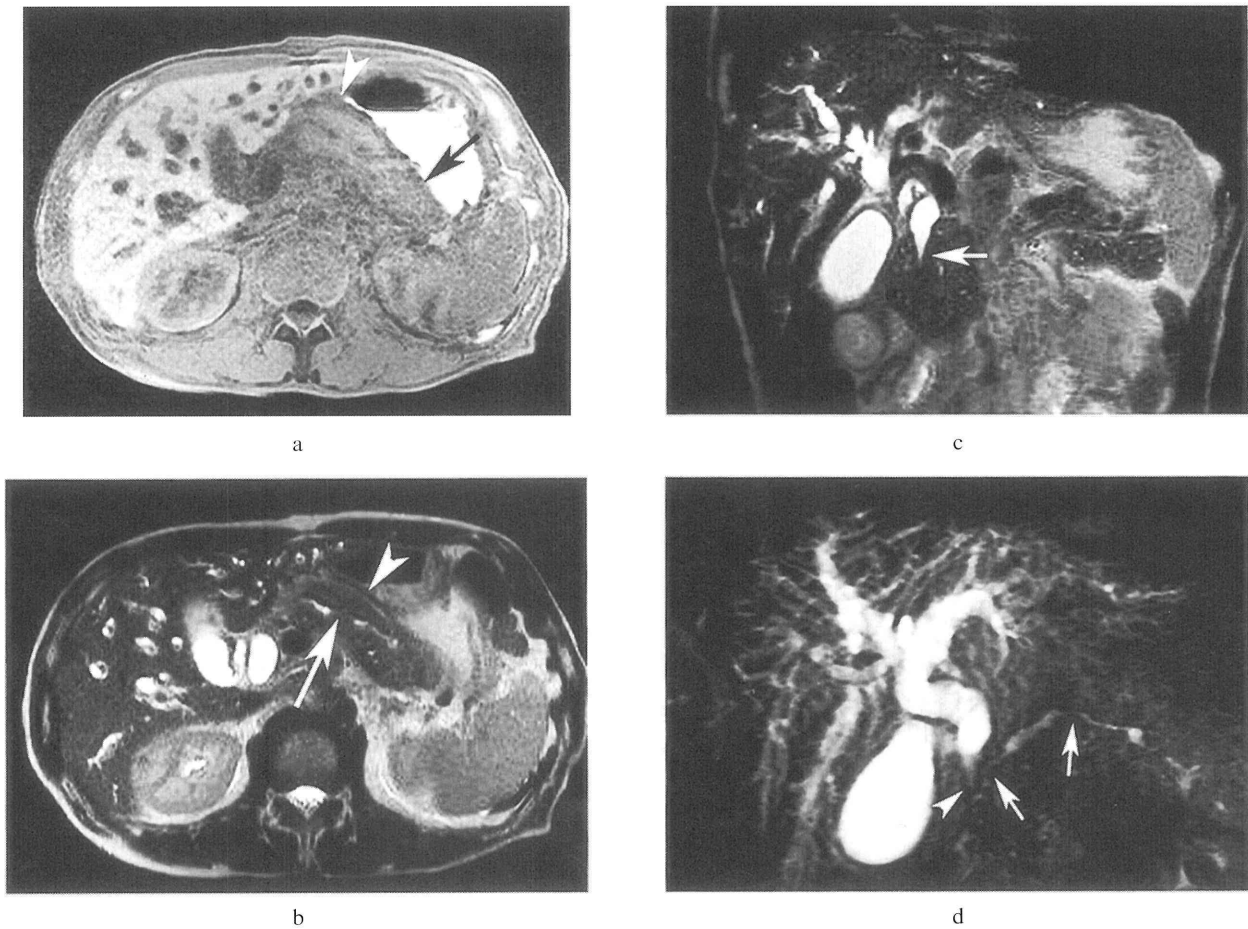
Because the patient had a history of bronchial asthma, abdominal contrast-enhanced computed tomography (CT) was not performed. Although abdominal plain CT revealed a sausage-like swelling over the entire pancreas, no findings were suggestive of inflammation extending into the surrounding fat tissues, which can be seen in acute pancreatitis. The main pancreatic duct showed partial, mild dilatation in the pancreatic body and tail, with no calcification. The common bile duct was significantly dilated, and the intrahepatic bile duct was also dilated (Fig. 1). Fat-suppressed T1-weighted (TIW) transverse images by abdominal magnetic resonance imaging (MRI) showed the overall pancreas to have a low signal intensity, with a hypointense band at the edge of the pancreatic body (Fig. 2a). T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE) transverse images showed narrowing of the main pancreatic duct in the pancreatic body, and similarly to fat-suppressed TIW images, a hypointense band at the edge of the pancreatic body (Fig. 2b). HASTE



**Fig. 1** Abdominal plain CT  
 a: transverse image at the level of the pancreatic body and tail  
 b: transverse image at the level of the pancreatic head  
 Sausage-like swelling was observed over the entire pancreas (arrows). The main pancreatic duct showed partial, mild dilatation in the pancreatic body and tail (black arrowhead). Dilatation of the common bile duct was significant (white arrowhead), and the intrahepatic bile duct was also dilated.

coronal images showed a smooth narrowing of the intrapancreatic portion of the common bile duct and marked dilatation in the central side of the biliary tract (Fig. 2c). MR cholangiopancreatography (MRCP) showed narrowing of the main pancreatic duct in the pancreatic head and body. The intrapancreatic portion of the common bile duct was also narrowed, and the common bile duct through the intrahepatic bile duct was significantly dilated (Fig. 2d). Diffusion-weighted images showed the overall pancreas to have mild high signal intensity, with an ADC value of  $1.11 \times 10^{-3}\text{ mm}^2/\text{sec}$ .

Autoimmune pancreatitis was suspected on the basis of the diagnostic imaging findings, but because the diffuse enlarged type of primary pancreatic malignant lymphoma was possible, levels of IgG and soluble inter-



**Fig. 2** MRI

a : Fat-suppressed T1-weighted transverse image

The overall pancreas appeared as a low signal intensity (black arrow) with a hypointense band at the edge of the pancreatic body (white arrowhead).

b : T2-weighted half-Fourier acquisition single-shot turbo spin-echo transverse image

A narrowed main pancreatic duct is visible in the pancreatic body (arrow), with a hypointense band at the edge similar to that seen in the fat-suppressed T1-weighted transverse image (arrowhead).

c : T2-weighted half-Fourier acquisition single-shot turbo spin-echo coronal image

The intrapancreatic portion of the common bile duct shows smooth narrowing (arrow), and marked dilatation can be observed in the central side of the biliary tract.

d : MR cholangiopancreatography

The main pancreatic duct was narrowed in the pancreatic head and body (arrows). In addition, the intrapancreatic portion of the common bile duct was narrowed (arrowhead), and significant dilatation was observed from the common bile duct through the intrahepatic bile duct (Fig. 2d).

leukin-2 receptor (sIL-2R) were measured. We found a high IgG level of 5,062 (870-1,700) mg/dL and a significantly elevated sIL-2R level of 2,220 (135-483) U/mL. Thus, the two diseases were difficult to differentiate.

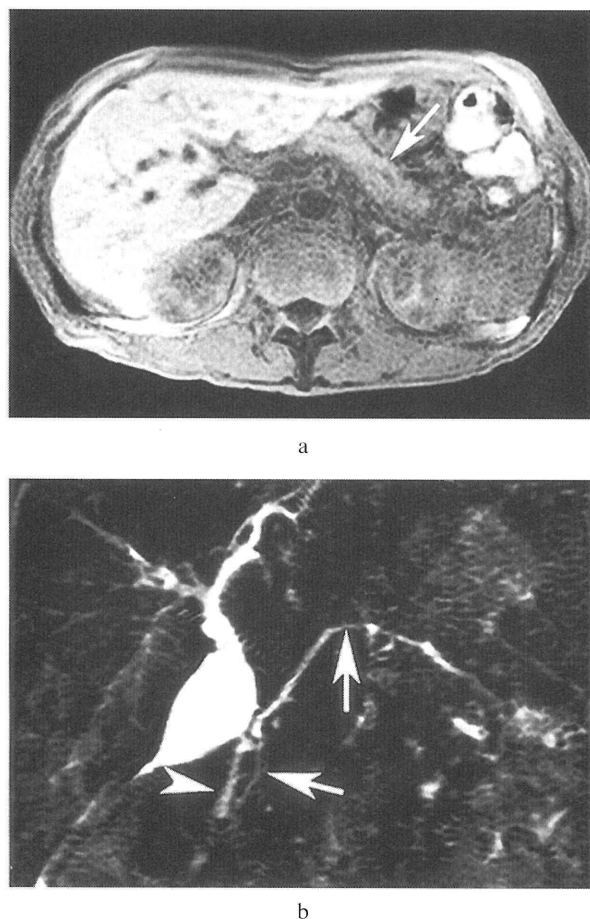
Gallium 67 scintigraphy detected no significantly abnormal accumulation image. Additionally, because a significantly elevated IgG4 level of 2,370 mg/dL (<157) was observed, autoimmune pancreatitis was diagnosed.

Steroid therapy improved the patient's symptoms. Fat-suppressed T1W transverse images showed a smaller pancreas with normalized signal intensity (Fig. 3a).

MRCP showed no narrowing of the main pancreatic duct. In addition, the narrowing of the intrapancreatic portion of the common bile duct resolved, and the dilatation of the biliary tract improved (Fig. 3b). Follow-up observations for about 3 years have detected no abnormal findings suggestive of recurrence.

**Discussion**

Sarles et al.<sup>3)</sup> reported the first case of high serum gammaglobulin with symptoms of pancreatitis in 1961. In Japan, Nakano et al.<sup>4)</sup> reported a patient with localized pancreatic swelling difficult to distinguish from pancreatic head cancer, and that significantly responded



**Fig. 3** MRI after steroid therapy  
 a : Fat-suppressed T1-weighted transverse image  
 The pancreas became smaller, with normalized signal intensity (arrow).  
 b : MR cholangiopancreatography  
 The narrowing of the main pancreatic duct resolved (arrow). In addition, the narrowing of the intrapancreatic portion of the common bile duct resolved (arrowhead), and the dilated biliary tract improved.

to steroid therapy in 1978. Yoshida et al.<sup>5)</sup> noted a patient with irregular narrowing of the main pancreatic duct showing mild symptoms of pancreatitis. They proposed that this disease, which responds to steroid therapy be defined as autoimmune pancreatitis in 1995. Since then, many patients with this disease have been reported, mainly in Japan, and the Japan Pancreas Society proposed its disease concept and diagnostic criteria in 2002<sup>1)</sup>. Thereafter, new diagnostic methods were established, and the diagnostic criteria were revised in 2006<sup>2)</sup>; the English version of these diagnostic criteria is described in the *Journal of Gastroenterology*<sup>6)</sup>. These clinical diagnostic criteria consist of the following three items :

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging

studies, such as abdominal ultrasonography, computed tomography, and magnetic resonance imaging.

2. High serum gammaglobulin, IgG, or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor.
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.

A diagnosis of autoimmune pancreatitis is established when criterion 1, together with criterion 2 and/or 3, are fulfilled. However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers.

The present patient also showed narrowing of the main pancreatic duct and diffuse enlargement of the pancreas, but because of the high sIL-2R level, primary pancreatic malignant lymphoma was initially suspected. High sIL-2R levels frequently occur in malignant lymphoma. However, Hamano et al.<sup>7)</sup> reported that 7 patients out of 8 with autoimmune pancreatitis had high sIL-2R levels; thus, it may be difficult to differentiate these two diseases based on the sIL-2R levels.

Since Hamano et al.<sup>8)</sup> reported in 2001 that elevated IgG4 levels can be found specifically in autoimmune pancreatitis patients, as many as 19 out of 20 patients (95%), many institutions have used measurement of the IgG4 level as a diagnostic marker for autoimmune pancreatitis. However, many studies currently report a positive rate of approximately 70%<sup>9-11)</sup>. In addition, because this level would be elevated in patients with pancreatic cancer, it should be handled carefully<sup>12)</sup>; there are no reports of high levels in patients with malignant lymphoma. The high IgG4 level in the present patient led to a diagnosis of autoimmune pancreatitis.

Findings of diagnostic imaging for autoimmune pancreatitis show sausage-like swelling of the pancreas, but the margin is clear with no change in the surrounding fat tissues, which are the points for distinguishing it from acute pancreatitis or the diffuse type of pancreatic cancer. Irie et al.<sup>13)</sup> reported that the characteristic finding of autoimmune pancreatitis is the capsule-like rim of the pancreas, and Eerens et al.<sup>14)</sup> also mentioned that T2-weighted images show it as a hypointense band. The latest report by Fujinaga et al.<sup>15)</sup> showed that CT could detect 13 out of 35 patients (37%), whereas MRI could detect it at a higher rate of 19 out of 25 patients (76%). Earlier studies often reported diffuse enlargement, but localized enlargement was also frequently found<sup>16)</sup>, and fat-suppressed T1W images reportedly showed pancreatic parenchyma as a low signal intensity in all patients<sup>15)</sup>. The present patient also showed sausage-like swelling with a clear margin, and fat-suppressed

TIW images showed a low signal intensity, which are typical autoimmune pancreatitis findings. In addition, fat-suppressed TIW images and HASTE images showed the capsule-like rim.

Various organs such as the salivary gland, lung, gallbladder, bile duct, kidney, intestinal tract, retroperitoneum, and lymph node have also been reported to have extrapancreatic lesions of autoimmune pancreatitis<sup>17)</sup>, of which complication with bile duct lesions is found most frequently. Nakazawa et al.<sup>18)</sup> classified these bile duct lesions into 4 types. Type 1, the most frequent, is only narrowing of the lower common bile duct, and our case was classified as Type 1.

In the present case, it was hard to distinguish the disease by diagnostic imaging from the diffuse enlarged type of primary pancreatic malignant lymphoma<sup>19)</sup>. From our own experience, patients with the diffuse enlarged type of primary pancreatic malignant lymphoma also showed a dilated biliary tract, diffuse enlargement of the pancreatic parenchyma, and a clear margin. In addition, mild dilatation and narrowing of the main pancreatic duct were observed, making it difficult to differentiate the disease by CT or conventional MRI. The gallium 67 scintigraphy performed in the present case showed no abnormal accumulation, but Saegusa et al.<sup>20)</sup> reported that substantial accumulation was observed in 16 out of 24 patients (67%) with autoimmune pancreatitis. Thus, the presence of accumulation cannot help differentiation. As mentioned previously, sIL-2R levels cannot be used as an absolute method for differentiation. Although the IgG4 level may be the most useful index for differentiation, it has the disadvantages, such as no insurance coverage and longer time needed for the results to be available in our facility. If the patient with diffuse enlargement of the pancreas reveals no laboratory evidence (particularly high serum IgG4) of autoimmune pancreatitis, Finkelberg et al.<sup>21)</sup> describe, in their diagnostic and treatment algorithm for autoimmune pancreatitis, that the endoscopic ultrasonography-guided fine-needle aspiration or biopsy becomes necessary for diagnosis.

The present patient with autoimmune pancreatitis had an ADC value of  $1.11 \times 10^{-3} \text{ mm}^2/\text{sec}$ . We found no published articles concerning ADC values in patients with autoimmune pancreatitis or primary pancreatic malignant lymphoma. Three patients with autoimmune pancreatitis we treated showed an ADC value of  $1.22 \pm 0.11 \text{ mm}^2/\text{sec}$ , and two patients with primary pancreatic malignant lymphoma showed low values of  $0.56 \times 10^{-3} \text{ mm}^2/\text{sec}$  and  $0.59 \times 10^{-3} \text{ mm}^2/\text{sec}$ . It has been reported that the entire tumor is visualized as a high signal intensity by diffusion-weighted images because malignant lymphoma in the brain has a higher cell density<sup>22)</sup>. The ADC value is reduced significantly

to  $0.58 \times 10^{-3} \text{ mm}^2/\text{sec}$  and can be distinguished from gliomas and metastasis<sup>23)</sup>. Also in the craniocervical region, it was reported that the ADC value of malignant lymphoma is only  $0.66 \times 10^{-3} \text{ mm}^2/\text{sec}$  and can be distinguished from carcinoma ( $1.13 \times 10^{-3} \text{ mm}^2/\text{sec}$ ) and benign solid tumor ( $1.56 \times 10^{-3} \text{ mm}^2/\text{sec}$ )<sup>24)</sup>. Because malignant lymphoma thus specifically exhibits low ADC values, this may be useful for distinguishing it from autoimmune pancreatitis.

### Conclusion

Autoimmune pancreatitis was mentioned in Current Concepts in Review Article in the *New England Journal of Medicine* in 2006<sup>21)</sup> and is a disease that is gathering worldwide attention. Here we report a case of autoimmune pancreatitis that was difficult to distinguish from the diffuse enlarged type of primary pancreatic malignant lymphoma by diagnostic imaging. For differentiating these two diseases, the IgG4 and ADC values were useful.

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## IgG4 と ADC 値が診断に有用であった自己免疫性膵炎の 1 例

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症例は 65 歳の男性。腹痛が強くなり、超音波検査で肝内胆管の拡張が認められたため入院となった。腹部単純 CT では膵臓は全体的にソーセージ様の腫大がみられ、胆道の拡張も認められた。MRI の脂肪抑制 T1 強調像では膵臓は全体的に低信号として描出され、体部の辺縁部に低信号帯が認められた。HASTE 像では膵体部で主膵管の狭窄がみられ、辺縁部には T1 強調像と同様に低信号帯が認められた。MRCP では膵頭部と体部の主膵管が狭小化していた。また、膵内総胆管も狭窄し、総胆管から肝内胆管の著明な拡張が認められた。拡散強調像では膵は全体的に軽度高信号となり、みかけの拡散係数値は  $1.11 \times 10^{-3} \text{ mm}^2/\text{sec}$  であった。soluble interleukin-2 receptor が高値を示したことからびまん性腫大型の膵原発悪性リンパ腫を疑ったが、IgG4 が著明に上昇したことから自己免疫性膵炎と診断された。

ステロイド治療が施行され、症状は改善した。脂肪抑制 T1 強調像では膵は縮小し、信号も正常化してきた。MRCP では主膵管の狭窄は消失した。また、膵内総胆管の狭窄も消失し、胆道の拡張も改善された。

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<キーワード> 自己免疫性膵炎、MRI、拡散強調画像、みかけの拡散係数値

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