

Long-term follow-up of patients with autoimmune pancreatitis revealed characteristics of chronic disease and recurrence

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Abstract

Autoimmune pancreatitis is a unique disease, characterized by lymphoplasmacytic inflammation in the acute stages. However, the active clinical features are unlikely to persist for longer periods. Through long-term follow-up, we investigated the disease course in 51 patients with autoimmune pancreatitis. We found recurrence in 21 (41%) and pancreatic stone formation in 9 (18%) patients. Pancreatic stone formation was significantly more frequent in the recurrence group (7/21; 33%), compared to the non-recurrence group (2/30; 7%). Moreover, we found high serum immunoglobulin-G4 concentrations in 13 of 175 (7.4%) patients with ordinary chronic pancreatitis. This suggested that pancreatic stone formation was closely associated with recurrence and that autoimmune pancreatitis may transform into ordinary chronic pancreatitis after several recurrences. We found that the immune complex level, with a cut-off value of 10 $\mu\text{g/dl}$, served as a good predictor of recurrence, with high sensitivity (61.9%), specificity (70.0%) and efficacy (66.7%). We also confirmed that human leukocyte antigen and cytotoxic T-lymphocyte antigen-4 polymorphism were useful predictors for autoimmune pancreatitis recurrence.

Introduction

Autoimmune pancreatitis (AIP) has been characterized by irregular narrowing of the main pancreatic duct (MPD) and sonolucent swelling of the parenchyma, both due to lymphoplasmacytic inflammation during the active stage of the disease. AIP has also been characterized by the absence of pancreatic stone formation.¹ These findings suggest that autoimmune pancreatitis is clearly distinguished from chronic pancreatitis, including alcohol-induced chronic pancreatitis, and has a distinctive disease profile. However, these pathological features are found in the acute stage of the disease; thus, it is unlikely that the inflammatory characteristic of this condition persists for longer periods. In a chronic form of the disease, we may find different features from those now generally recognized. Furthermore, AIP is generally found in older people with suppressed immuno-surveillance systems; consequently, these patients may be susceptible to various malignant diseases.

To clarify these issues, we conducted long-term follow-ups of AIP, and we investigated four topics: (1) outcome, recurrence and pancreatic stone formation, (2) the ability of AIP to transform into chronic pancreatitis, (3) prediction of recurrence by serum markers, and (4) association of AIP with malignancies.

1. Outcome, recurrence, and pancreatic stone formation.

We performed long-term follow-ups for 51 patients with AIP to assess outcomes.² The observation periods were 24-178 months (mean 72 months). Corticosteroid therapy was administered to 42 patients. During the long-term follow-up, 21 patients (41%) showed recurrences that required a second course of corticosteroid therapy (Fig.1).

We previously reported that a high serum immunoglobulin-G4 (IgG4) concentration was frequently and specifically found in AIP, representing disease activity.³ For these 51 patients, we found that the serum IgG4 concentration remained slightly high in over 60% of patients, though they were in a clinically inactive state after corticosteroid therapy.⁴ This

suggested that the active inflammatory process may persist even when patients are in a clinically inactive state; these conditions may facilitate recurrences.

We found pancreatic stone formation in 9 of 51 patients (18%). Among the 21 patients with recurrence, 7 (33%) exhibited pancreatic stone formation; in contrast, pancreatic stones were found in only 2 of the 30 (7%) patients in the non-recurrence group (Fig. 1). Accordingly, pancreatic stone formation was judged to be closely associated with recurrence.² Previous studies investigated the recurrence of AIP, but they reported lower recurrence rates, ranging from 6 to 23 %.⁵⁻⁷ Though the exact reasons for these discrepancies are unclear, they may be related to the number of patients, the follow-up periods, and the type of corticosteroid therapy may be related.

Though a previous study reported that the absence of pancreatic stones is a characteristic of autoimmune pancreatitis,¹ the potential for forming pancreatic stones is not absent in AIP.^{2,6} Incomplete obstruction of the main pancreatic duct system and the stasis of pancreatic juice may give rise to the formation of pancreatic stones. The finding of irregular narrowing or stricture of the main pancreatic duct in patients with AIP provided further support for this potential mechanism. In addition, recurrent attacks may have intensified incomplete obstruction of the duct system and caused pancreatic juice stasis, which could have facilitated stone formation; however, we lack evidence to confirm this hypothesis.

One patient with AIP exhibited a pancreatic stone after several recurrences. In June 1996, a 55-year-old male was admitted to our hospital presenting with epigastralgia. His serum amylase level was elevated to 3000 U/l, and he was diagnosed with acute pancreatitis. Next, obstructive jaundice appeared. His serum IgG4 concentration had risen to 486 mg/dl, and endoscopic retrograde pancreatography (ERP) showed irregular narrowing in the pancreatic head region (Fig. 2 a). He was diagnosed with AIP, and steroid therapy was administered. This resulted in amelioration of the ERP finding and lowered the IgG4 levels to 213 mg/dl. In August 1998, the patient showed jaundice and obstruction of the common bile duct by

ERC, but there was no swelling of the pancreatic parenchyma or irregular narrowing of the main pancreatic duct (MPD). Serum IgG4 was dramatically elevated to 1135 mg/dl. He was diagnosed with recurrence, primarily in the bile duct lesion. Steroid therapy was administered, and this resulted in the amelioration of the bile duct obstruction. Ten years after the onset, in February 2006, the patient complained of epigastralgia, and ERP showed a narrowing in the body region of the MPD and dilatation in the tail region (Fig. 2 b). At that time, he was prescribed prednisolone at a maintenance dose of 2.5 mg. An increase of prednisolone to 20mg ameliorated the MPD narrowing and dilatation. However, after a reduction of the prednisolone dose, a pancreatic stone appeared in the body and tail regions of the MPD (Fig. 2 c). This case supported the hypothesis that multiple recurrences and the resulting MPD stenosis and pancreatic juice stasis may induce pancreatic stone formation. It also showed that high IgG4 concentrations corresponded to recurrence, and clearly indicated the active stage of AIP.

On the other hand, we also experienced a patient with AIP that had low serum IgG4 concentrations and no recurrences during 10 years of follow-up. In November 1997, a 65-year-old female was admitted to an affiliated hospital, presenting with epigastralgia, obstructive jaundice, and pancreatic head swelling. She was diagnosed with pancreatic cancer. However, an endoscopic retrograde cholangiopancreatography (ERCP) showed diffuse irregular narrowing of the MPD, suggesting a diagnosis of AIP (Fig. 2 d). Her serum IgG4 value was 42 mg/dl and her serum antinuclear antibody (ANA) level was x160. She was diagnosed with AIP and given corticosteroid therapy, which ameliorated these findings. During the 10-year follow-up, she showed no serum elevation of IgG4 and no abnormal image findings, including pancreatic swelling, that would have suggested recurrences. Magnetic resonance imaging (MRI) (Fig. 2e) and MRCP (Fig. 2f) also showed no progression or duct changes during those 10 years. Furthermore, she exhibited no pancreatic stone formation. Accordingly, this case suggested that a normal IgG4 concentration during

long-term follow-up periods accurately represented an inactive state and no disease progression. This also suggested that low serum IgG4 concentrations may be considered an indication for the cessation of maintenance corticosteroid therapy.

2. AIP can transform to chronic pancreatitis

The results of this long-term follow-up suggested that some patients with AIP were complicated with pancreatic stones after several attacks of recurrence. This suggested that some cases of AIP may have transformed into ordinary chronic pancreatitis. If true, the next question was whether AIP was a precursor of ordinary chronic pancreatitis. We considered serum IgG4 elevation to be a serological marker of AIP, even at chronic or advanced stages, because over 60% of patients with AIP maintained high serum IgG4 concentrations after their clinical symptoms had resolved.⁴ To investigate whether AIP might result in ordinary chronic pancreatitis, we measured serum levels of IgG4 in 175 patients with chronic pancreatitis that had been diagnosed before 1995, the year that AIP was first described.¹ We found high serum IgG4 concentrations in 13 of 175 patients with ordinary chronic pancreatitis (7.4%), (12 males and 1 female, mean age 56 years; 9 alcoholic and 4 idiopathic). Of the 13 patients, 3 had been diagnosed for the first time with pancreatic cancer, and 1 had been recently diagnosed with AIP. The remaining 9 patients showed typical findings of ordinary chronic pancreatitis, including pancreatic stones or irregular dilation of the MPD (Fig. 3). This suggested that an advanced stage of AIP may result in ordinary chronic pancreatitis. It did not rule out the possibility that AIP may represent an early stage of ordinary chronic pancreatitis.⁸ Consistent with our results, a previous study found that serum IgG4 was elevated in sera of 11.9% of patients with ordinary chronic pancreatitis.⁹

3. Prediction of recurrence by serum markers

Various serum markers and genetic markers have been reported to be associated with the

recurrence of AIP. We found that, for monitoring AIP, both IgG4 and the immune complex (IC), determined by the monoclonal rheumatoid factor method, were useful markers.

In the clinical course of a 69-year-old woman, we found two recurrences in which serum elevations of IC and IgG4 preceded the overt appearance of clinical recurrence by several months. This indicated that, in addition to IgG4, IC can sensitively predict recurrence and represent disease activity.⁸ We then investigated various serum markers for their efficacy in predicting recurrences by comparing the levels of various markers in recurrence and non-recurrence groups. We found the IC value, as determined by the monoclonal rheumatoid method (IC-mRF), was significantly higher at onset in the recurrence group compared to the non-recurrence group. Using a cut-off value of 10 µg/dl, IC-mRF performed well in predicting recurrence, with good sensitivity (61.9%), specificity (70.0%) and efficacy (66.7%). The probability of recurrence was 60% when IC-mRF>10 µg/dl, and 30% when IC-mRF<10 µg/dl.

Complement factors C3 and C4 have also been reported as useful markers for monitoring disease activity or tissue damage. We found decreased serum C3 or C4 levels in 35% and 37% of AIP patients, respectively. This suggested that complement activation may play a role in the pathogenesis of AIP.¹⁰ We compared the serum levels of C3 and C4 in patients with high serum IC and those with normal IC levels. Serum C4 was significantly lower and serum C3 tended to be lower in the high IC group compared to the normal IC group.¹⁰ These results, together with the IC data, suggested that a classical pathway may be operating in some AIP patients. In turn, this suggested that high serum IC may be useful for predicting both tissue damage and the probability of recurrence. A report by Kubota et al. showed that high serum IgG, diffuse pancreatic swelling, and low bile duct stenosis were more frequently observed in patients that had relapsed. A logistic regression analysis showed that diffuse pancreatic swelling was a predictor of recurrence.¹¹

Specific human leukocyte antigen (HLA) polymorphisms were also reported to predict

the recurrence of AIP and acted as primary determinants of autoimmune hepatitis susceptibility or relapse.¹² Furthermore, substitution of an aspartic acid at position 57 of the HLA designated DQ β 1 (DQ β 1 57) was reported to affect the recurrence of AIP. Thus, Park et al. examined associations between the onset of AIP recurrence and the density of nonaspartic acids at DQ β 1 57. They observed in patients that experienced a recurrence, that homozygosity of nonaspartic acids was associated with a significantly earlier onset of recurrence compared to heterozygosity of nonaspartic acids.¹²

The cytotoxic T-lymphocyte antigen 4 (CTLA4) polymorphism has been reported to be another predictor of AIP recurrence.¹³ CTLA4 is an inhibitory receptor expressed on the cell surface of activated-memory T cells and on regulatory T cells; it acts largely as a negative regulator of T-cell responses by modulating positive T-cell costimulatory signals on antigen-presenting cells. Single nucleotide polymorphisms (SNPs) in CTLA4, termed +49A/G, have been specifically associated with susceptibility to autoimmune diseases, including type 1 diabetes, autoimmune thyroid disease, autoimmune hepatitis, and primary biliary cirrhosis. To investigate whether CTLA4 was associated with AIP pathogenesis in our cohort, we determined the presence of four CTLA4 gene SNPs in patients with AIP and healthy controls. We detected SNP +6230G/G significantly more frequently in patients with AIP than in healthy subjects. In addition, we found that the +49A/A and +6230A/A genotypes were associated with an enhanced risk of recurrence.¹³

4. AIP and malignancies

AIP is generally found in older people with suppressed immuno-surveillance systems that consequently have elevated susceptibility to various malignant diseases. To date, among 51 AIP patients, we found 11 malignant lesions in 9 patients (17.6%); these included malignant lymphoma, lung cancer, hepatocellular carcinoma, renal carcinoma, breast cancer, duodenal cancer, colon cancer, prostate cancer, and ovarian cancer. These findings were consistent

with other reports that found various malignant lesions complicated with AIP.^{6,14-16} Some malignancies may occur during or after maintenance therapy with corticosteroid, suggesting that a steroid-induced immuno-suppressive state may induce malignant lesions. Because we had no age-matched controls, we could not determine whether AIP represented a significantly higher risk for malignant diseases. Incidentally, it is important to differentiate between AIP and pancreato-biliary malignancies. Bile duct cancer was reported to be complicated with AIP,¹⁶ thus, the co-occurrence of bile duct cancer should be investigated, even with a confirmed diagnosis of AIP.

Twelve cases of pancreatic cancer complicated with AIP have been previously reported¹⁷⁻²¹ Among the 12 cases, 5 occurred concurrently with AIP, and 7 occurred from 3 to 5 years after the diagnosis of AIP. It has been estimated that, generally, two thirds of pancreatic cancers occur in the head region. Surprisingly, 9 of the 12 tumors (75%) complicated with AIP were located in the body and tail regions of the pancreas, including 3 in the head, 5 in the body, 3 in the tail, and 1 in the body and tail regions. Accordingly, the occurrence of a tumor in the body and tail of the pancreas may be a characteristic finding of pancreatic cancer complicated with AIP (Tanaka S et al., *Suizo* 2007;22:663-71 in Japanese). In addition to the immuno-suppressive state, a chronic inflammatory process similar to ordinary chronic pancreatitis may evoke pancreatic malignancy.²² Though the exact prevalence is unknown, a careful follow-up with tumor marker is mandatory.

In conclusion, our findings showed that 40% of patients with AIP had recurrences during long-term follow-up. Many patients had been treated with prednisolone at onset due to the highly active state of the disease. We observed that, although, the disease appeared to be clinically inactive during or after maintenance therapy, relapse was likely to occur, and that long-term therapy was required. To prevent clinical relapse, corticosteroid therapy should be restarted at an early subclinical stage of relapse, and reliable parameters must be identified

for predicting relapse. Among several possible serum markers, we found that the IC-mRF value showed significant elevation in the recurrence group, suggesting that IC may be useful for predicting the recurrence of AIP. Furthermore, a normal IgG4 value represented the inactive state and may be an indicator for the cessation of maintenance corticosteroid therapy. Some patients with AIP exhibited complications with pancreatic stones after several attacks of recurrence. Thus, autoimmune pancreatitis appeared to transform into a form of chronic pancreatitis. Autoimmune pancreatitis may also be complicated with a variety of malignant lesions. To date, 12 cases of pancreatic cancer complicated with AIP have been reported, with a preponderance in body and tail regions of the pancreas. Though AIP should be carefully differentiated from pancreatic cancer, we recommend checking for the co-occurrence of pancreatic cancer even when a diagnosis of AIP is confirmed.

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Figure legends

Fig.1 Outcome of long-term follow up for 51 patients with autoimmune pancreatitis. Observation periods lasted for 24-178 months (mean 72 months).

Fig. 2 Image findings from a 55-year-old male with autoimmune pancreatitis that had high serum IgG4 concentrations. A pancreatic stone appeared after several recurrences during a 10-year follow-up. (a) Endoscopic retrograde pancreatography (ERP) at onset showed irregular narrowing of the head region of the pancreas, (b) 10 years after onset, ERP image of the main pancreatic duct (MPD) showed narrowing in the body and dilatation in the tail region, (c) Pancreatic stone appeared in the body and tail regions of the MPD after a reduction in the prednisolone dose. For comparison, the right panels show image findings for a 65-year-old female with autoimmune pancreatitis that had normal serum IgG4 concentrations during 10 years of follow-up. (d) an ERP performed at onset showed diffuse irregular narrowing of the MPD, (e) a MRI and (f) MRCP of the pancreas showed no progression or duct changes in the 10 years of follow-up periods.

Fig. 3 Endoscopic retrograde cholangiopancreatography (ERCP) of an 84-year-old male with alcoholic chronic pancreatitis that had a high serum IgG4 concentration (585 mg/dl).

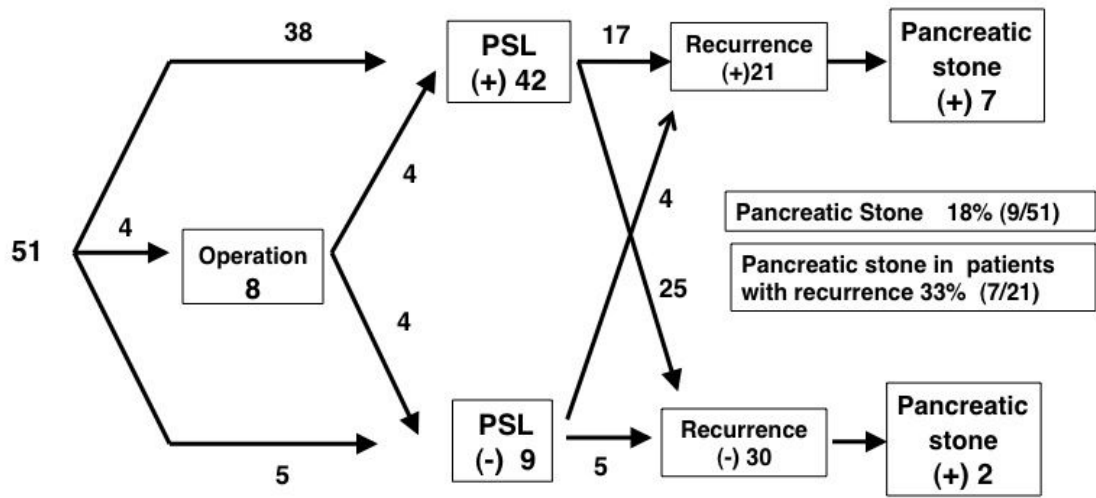


Fig. 1

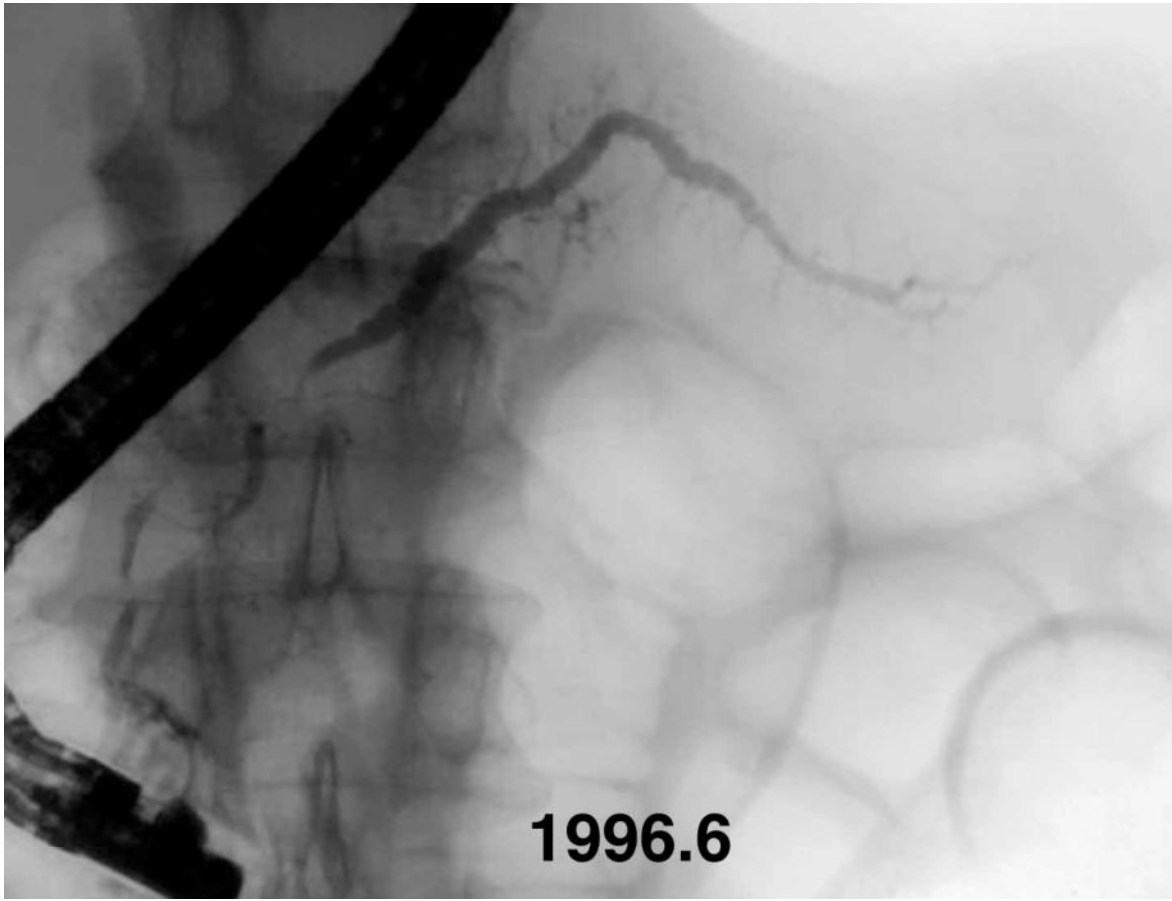


Fig. 2a

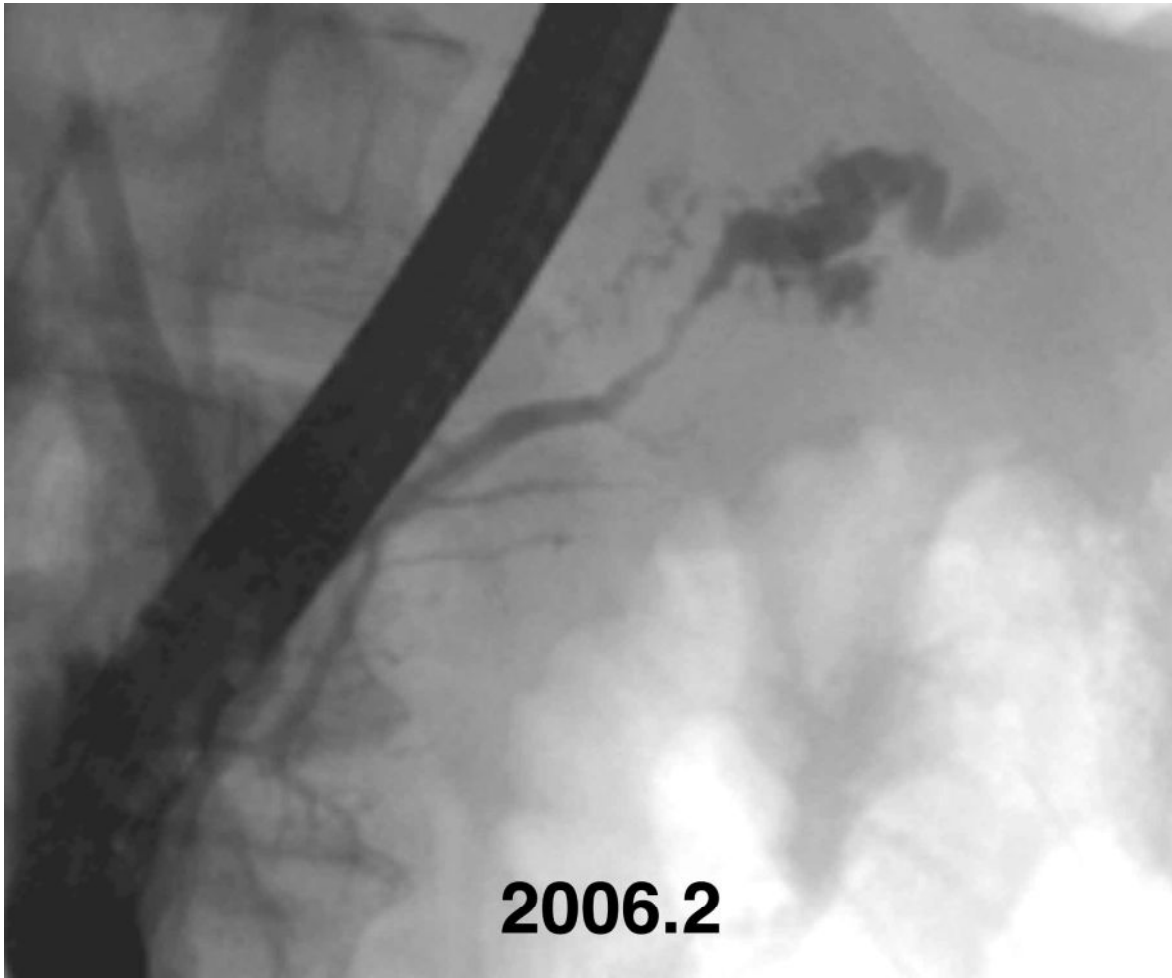


Fig. 2b

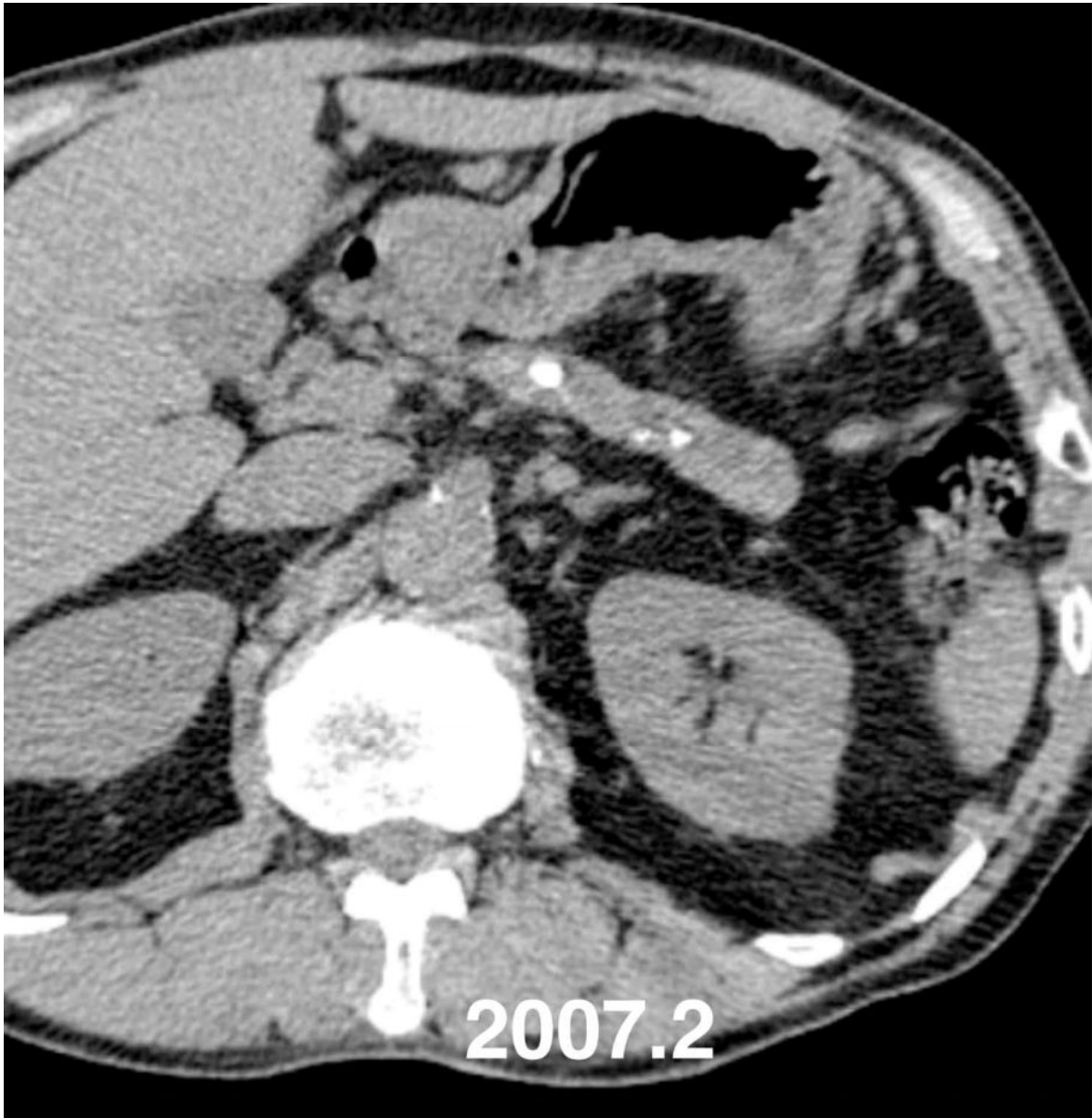


Fig. 2c

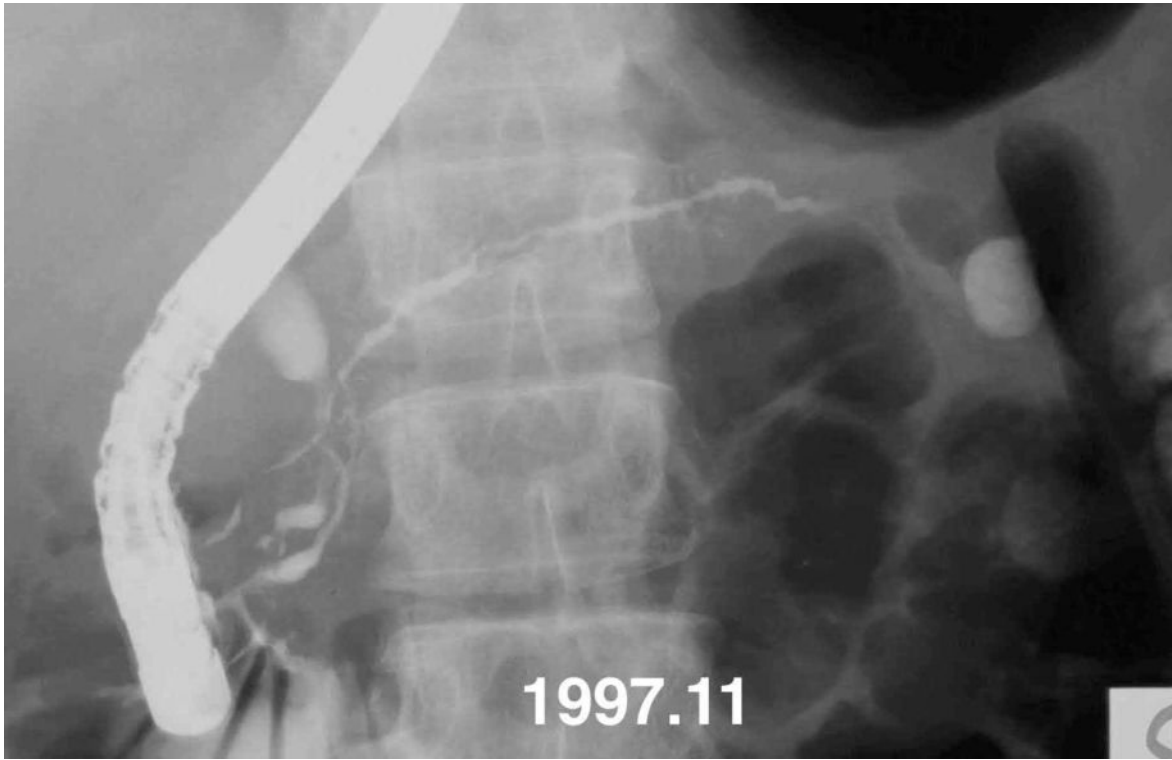


Fig. 2d



Fig. 2e

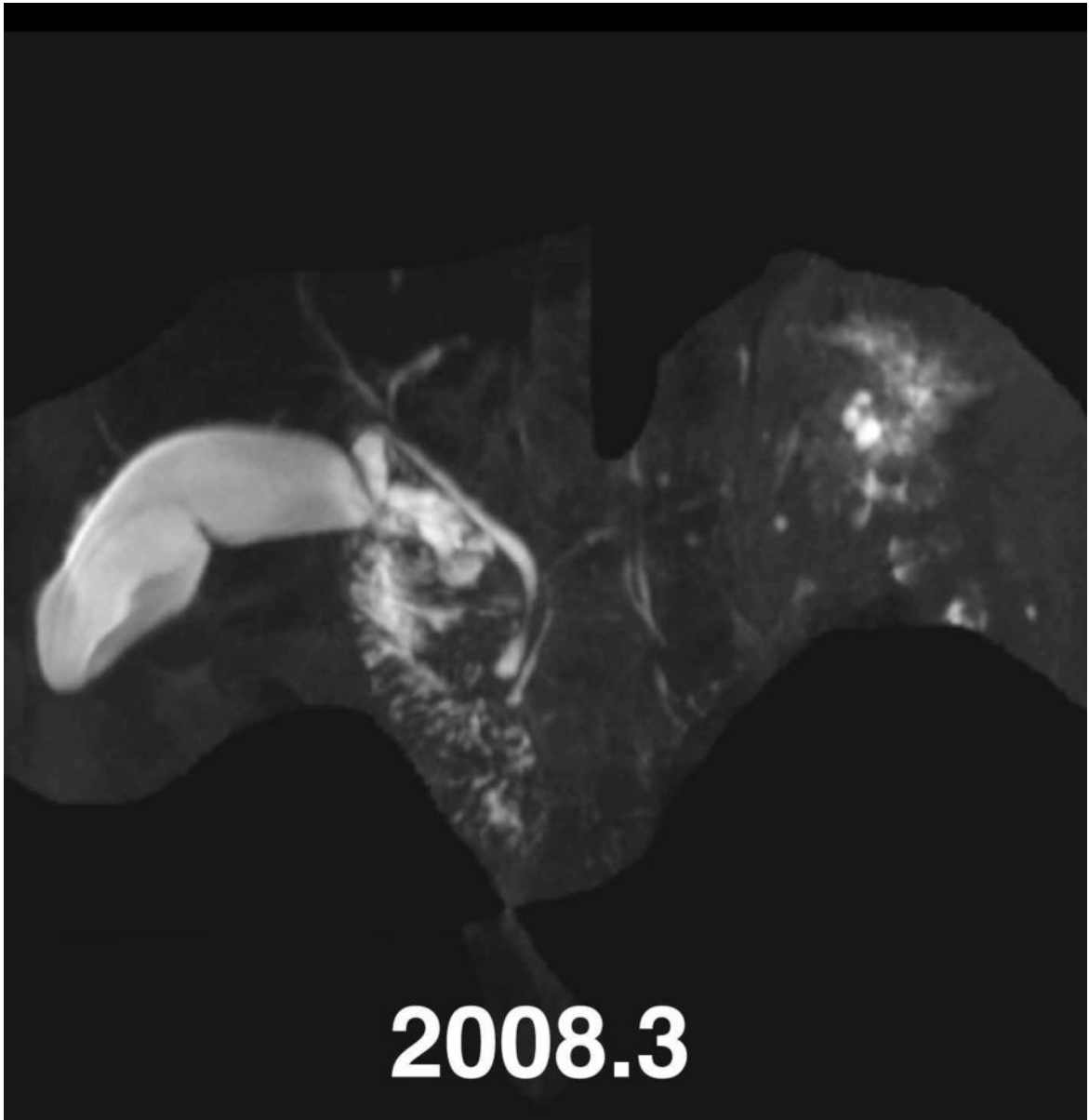


Fig. 2f



Fig. 3