

## Modification of Management Algorithm of Radiologically Suspected Pancreatic and Biliary Malignancy by Incorporation of Local Experience of Autoimmune Pancreatitis

CYH Chan<sup>1</sup>, DHS Fung<sup>1</sup>, VWT Chan<sup>1</sup>, OK Wong<sup>2</sup>, SKY Kwok<sup>1</sup>, WK Wong<sup>1</sup>, KW Tang<sup>1</sup>

Departments of <sup>1</sup>Radiology and Imaging and <sup>2</sup>Pathology, Queen Elizabeth Hospital, Jordan, Hong Kong

### ABSTRACT

**Objectives:** To review the clinical and pathological features of autoimmune pancreatitis (AIP) in a tertiary referral centre in Hong Kong, and to determine preoperative factors that facilitate diagnosis of AIP in order to avoid Whipple's procedure.

**Methods:** According to our pathology and radiology databases, 13 patients were diagnosed in our hospital with type 1 AIP from 1 January 2003 to 31 December 2013. Clinical, serological, radiological and histopathological features and treatment outcomes were analysed.

**Results:** The mean age of patients was 63.2 years with a male predominance (85%). Obstructive jaundice was the most common presenting symptom (69%). Serum immunoglobulin G4 (IgG4) was measured in 12 patients and was elevated in all cases. Focal pancreatic mass was the most common radiological manifestation (46%), followed by diffuse (31%) and segmental (23%) swelling of the pancreas. Subgroup analysis of subjects diagnosed only after surgery showed significant elevation of postoperative serum IgG4 level, with extrapancreatic manifestations present in two cases.

**Conclusions:** In this cohort, our AIP patients showed similar features with those in China and Taiwan, but different to those in Japan and Korea. A future large-scale multicentre cohort would help determine whether AIP manifests differently in different geographical locations. AIP can mimic pancreatic and biliary malignancies, thus radiologists should be familiar with its typical radiological features. Serum IgG4 should be measured and extra-pancreatic manifestations looked for in patients who manifest with radiologically suspected pancreatic cancer or extrahepatic cholangiocarcinoma at the pancreatic level. Judicious use of endoscopic ultrasound-guided biopsy, endoscopic retrograde pancreatography, and steroid trial in selected cases would be valuable to exclude malignancy and confirm AIP. Some Whipple's procedures can hopefully be avoided by these measures.

**Key Words:** Autoimmune diseases; Immunohistochemistry; Pancreatitis

### 中文摘要

## 按本地對自身免疫性胰腺炎的診治經驗修改對懷疑胰腺和膽道惡性腫瘤患者的診治方法

陳彥豪、馮漢盛、陳偉達、黃安傑、郭啟欣、王旺根、鄧國穎

**目的：**回顧香港一所三級醫院內自身免疫性胰腺炎（AIP）患者的臨床和病理學特徵。並探討患者術

**Correspondence:** Dr Cyrus YH Chan, Department of Radiology and Imaging, Queen Elizabeth Hospital, 30 Gascoigne Road, Jordan, Hong Kong.

Email: cyhchan2007@yahoo.com.hk

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前特徵以加快AIP診斷及避免Whipple手術。

**方法：**根據本院的病理和放射學資料庫，在2003年1月1日至2013年12月31日期間共有13宗AIP確診病例；按其臨床、血清學、放射學和組織病理學的特徵和治療結果進行分析。

**結果：**患者平均年齡63.2歲，男性居多（85%）。最常見的症狀是梗阻性黃疸（69%）。12名患者接受血清免疫球蛋白G4（IgG4）的檢測，水平升高。最常見的放射性表現為胰腺局部腫塊（46%），其次為胰臟瀰漫性腫大（31%）和節段性腫大（23%）。術後才被確診為AIP的患者術後血清IgG4水平顯著上升，其中兩例有胰外表現。

**結論：**本研究顯示本港AIP患者的表現特徵與中國大陸和台灣的患者相似，而與日本和韓國的患者有分別。進一步大型多中心研究將會有助於確定AIP患者的表現特徵是否在不同的地理位置有所不同。AIP與胰腺和膽道惡性腫瘤相似，因此放射科醫生必須掌握其影像學特徵。對於一些影像學懷疑胰腺癌或肝外膽管癌的病理，應測量病人的血清IgG4，並確定是否有胰外表現。審慎地使用內鏡超聲引導下穿刺活檢和內鏡逆行胰膽管造影，並在經揀選的情況下使用類固醇試驗治療，可以確診AIP和排除惡性腫瘤的可能性，並藉此避免Whipple手術。

## INTRODUCTION

Autoimmune pancreatitis (AIP) has been an increasingly recognised disease entity in recent decades, characterised by its autoimmune manifestations on clinical, histological, and laboratory grounds. It can sometimes be difficult to differentiate AIP from pancreatic adenocarcinoma or cholangiocarcinoma, and AIP accounts for 2% to 6% of resected pancreas for suspected pancreatic cancer.<sup>1</sup> Numerous papers about AIP have been published in Japan, Korea, and western countries.<sup>2-4</sup> Nonetheless literature about AIP in Hong Kong is scarce.<sup>5</sup> In this study, we aimed to review the clinical features of AIP in a regional tertiary referral centre in Hong Kong; and to specifically examine cases primarily diagnosed by histology of surgical specimens, and determine whether preoperative findings would have been sufficient to diagnose AIP and avoid unnecessary major surgery.

## METHODS

All patients diagnosed with AIP in our centre over the past decade were analysed. “Autoimmune pancreatitis”, “IgG4 related sclerosing pancreatitis”, and “lymphoplasmacytic sclerosing pancreatitis” were used as key words to search our Radiology Information System and the pathology database. Thirteen cases were identified during the period of 1 January 2003 to 31 December 2013.

Clinical features and treatment outcomes were retrieved from the Clinical Management System and analysed. They included demographics, presenting symptoms,

and extrapancreatic manifestations; serology, including serum immunoglobulin (Ig) G4 and IgG levels; imaging features, including ultrasonography (USG), computed tomography (CT), magnetic resonance imaging, positron emission tomography (PET), endoscopic retrograde cholangiopancreatography; histopathology, including lymphoplasmacytic infiltration, interstitial storiform fibrosis, obliterative phlebitis, raised IgG4 positive cells, and IgG4:IgG ratio.

Subgroup analysis was performed to look into cases diagnosed only after surgery. Parenchymal imaging, ductal imaging, serology, other organ involvement, histology of the pancreas, and response to steroid were assessed and the international consensus diagnostic criteria (ICDC) applied to evaluate whether preoperative findings were sufficient to make the diagnosis and avoid surgery.

## RESULTS

### Demographics and Presenting Symptoms

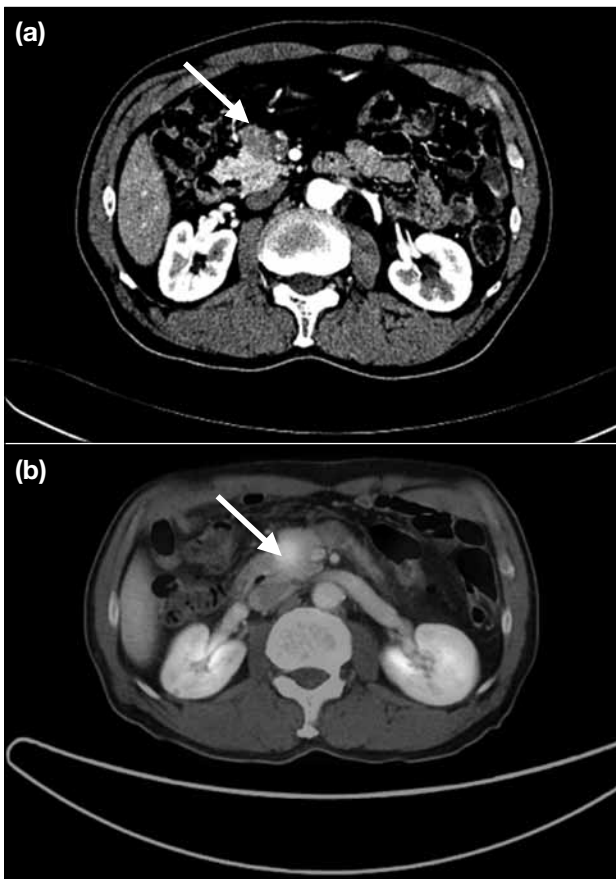
A total of 13 patients were diagnosed with type 1 AIP during the study period. Their mean age was 63.2 years, with a male predominance (85%). Obstructive jaundice (69%) was the most common presenting symptom, followed by epigastric discomfort (54%) and weight loss (46%).

### Serology

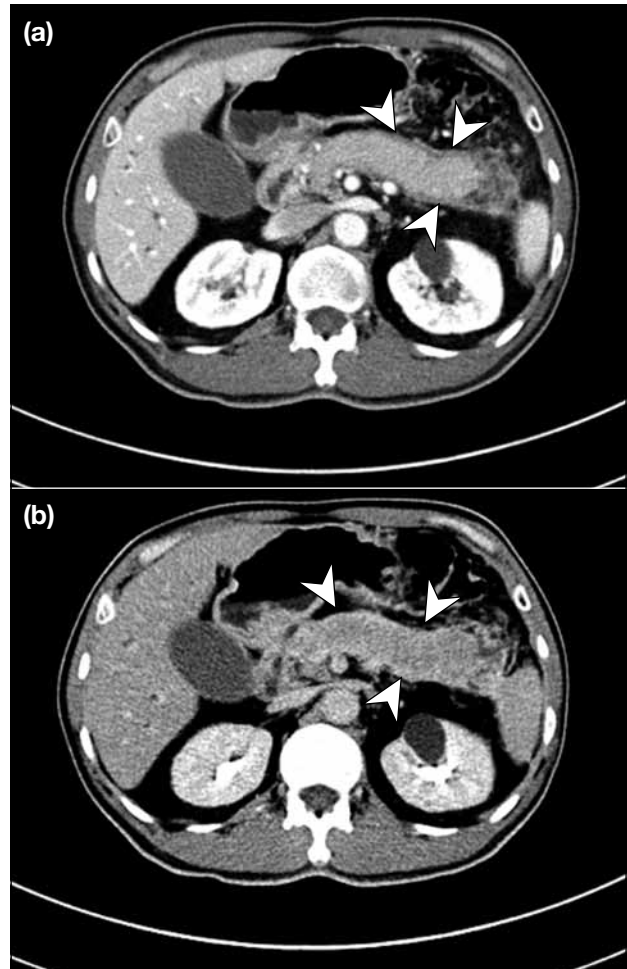
Serum IgG4 was measured in 12 patients and was elevated in all cases (324.5-10,500 mg/dl; mean, 1627 mg/dl). Serum IgG was measured in 10 patients and elevated in nine (1040-5020 mg/dl; mean, 2987 mg/dl).

### Radiology

Focal pancreatic mass accounted for 46% of cases, which was the most frequent radiological manifestation (Figure 1). It was usually hypoechoic on USG and hypoenhancing on CT, but could also be hypermetabolic on PET study. A solitary mass accounted for the majority of cases (83%), but multiple masses were also observed (17%). Pancreatic head was the most frequently involved location (100%), while neck involvement was also noticed in one subject. Nonetheless, classic, diffuse pancreatic swelling with featureless border (Figure 2) was seen in only four (31%) cases. ‘Capsule-like rim’, described as a hypodense halo surrounding the pancreas, was only seen in two (15%) cases. Significant peri-pancreatic stranding, which typically occurs in acute pancreatitis, was not seen in any case. Segmental swelling of the pancreas was identified in 23% of patients (Figure 3). This finding could be subtle, and patients might be misdiagnosed



**Figure 1.** Focal pancreatic mass. (a) An abdominal computed tomographic scan with contrast shows a focal hypoenhancing mass in the head of pancreas (arrow). (b) Positron emission tomography–computed tomography shows hypermetabolic activity of the mass (arrow). Histology later confirms autoimmune pancreatitis.



**Figure 2.** Diffuse enlargement of pancreas with capsule-like rim. (a) Portovenous phase and (b) delay phase images of computed tomographic abdomen with contrast show diffuse swelling of pancreas with featureless border, typical of diffuse-type autoimmune pancreatitis (AIP). Classic ‘capsule-like rim’ sign is shown as hypodense halo with delayed enhancement surrounding the pancreas (arrowheads). It is highly specific to AIP and is believed to represent fibrosis and inflammation surrounding pancreas.



**Figure 3.** Segmental swelling of head of pancreas. An abdominal computed tomographic scan with contrast shows focal bulging in the head of pancreas, which is iso-enhancing to the rest of pancreatic parenchyma (curved arrow).

with cholangiocarcinoma if there was stricture of the lower common bile duct. The Table summarises the imaging findings of our subjects.

### Other Organ Involvement

Extrapancreatic manifestation was extremely common in our patients (Figure 4). All of them showed one or more extrapancreatic manifestations. The biliary system, in particular the lower part of the common bile duct, was the most frequent site of involvement (85%). Intrahepatic or proximal bile duct stricture was not seen in any case. Retroperitoneal fibrosis ( $n = 1$ ), renal ( $n = 3$ ), salivary gland ( $n = 2$ ), and lacrimal gland ( $n =$

1) involvement were identified. Other organs affected included lymph node, gallbladder, duodenum, and urethra.

### Histopathology

Histopathology was obtained in eight cases. Lymphoplasmacytic infiltration and interstitial storiform fibrosis were present in all cases, while obliterative phlebitis was found in only half of the patients (Figure 5). Abundant IgG4 or raised IgG4:IgG ratio was noticed in 88% of cases.

### Treatment Outcomes

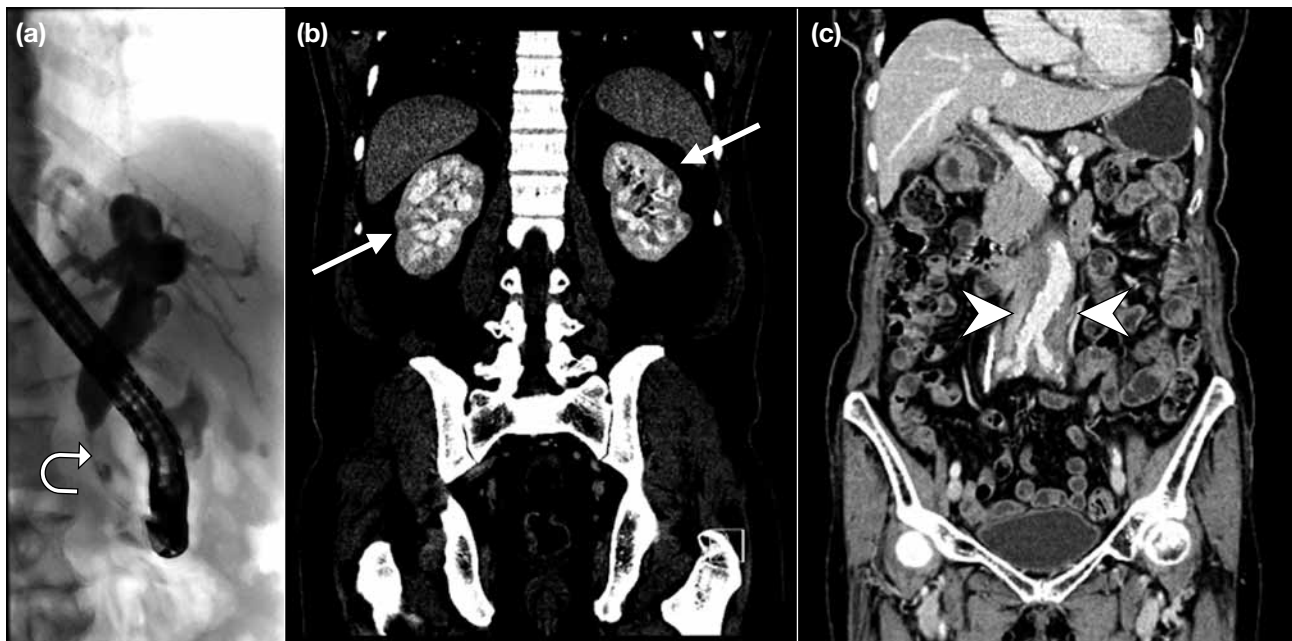
Surgery was performed in eight patients: Whipple's procedure in six, pylorus-preserving pancreaticoduodenectomy in one, and hepaticojejunostomy with cholecystectomy in one. Steroid therapy was the sole treatment in four patients; all of them had clinical, radiological, or serological response soon after initiation of therapy. Treatment was refused by one patient due to incidental remission of symptoms.

### Subgroup Analysis of Cases Only Diagnosed after Surgery

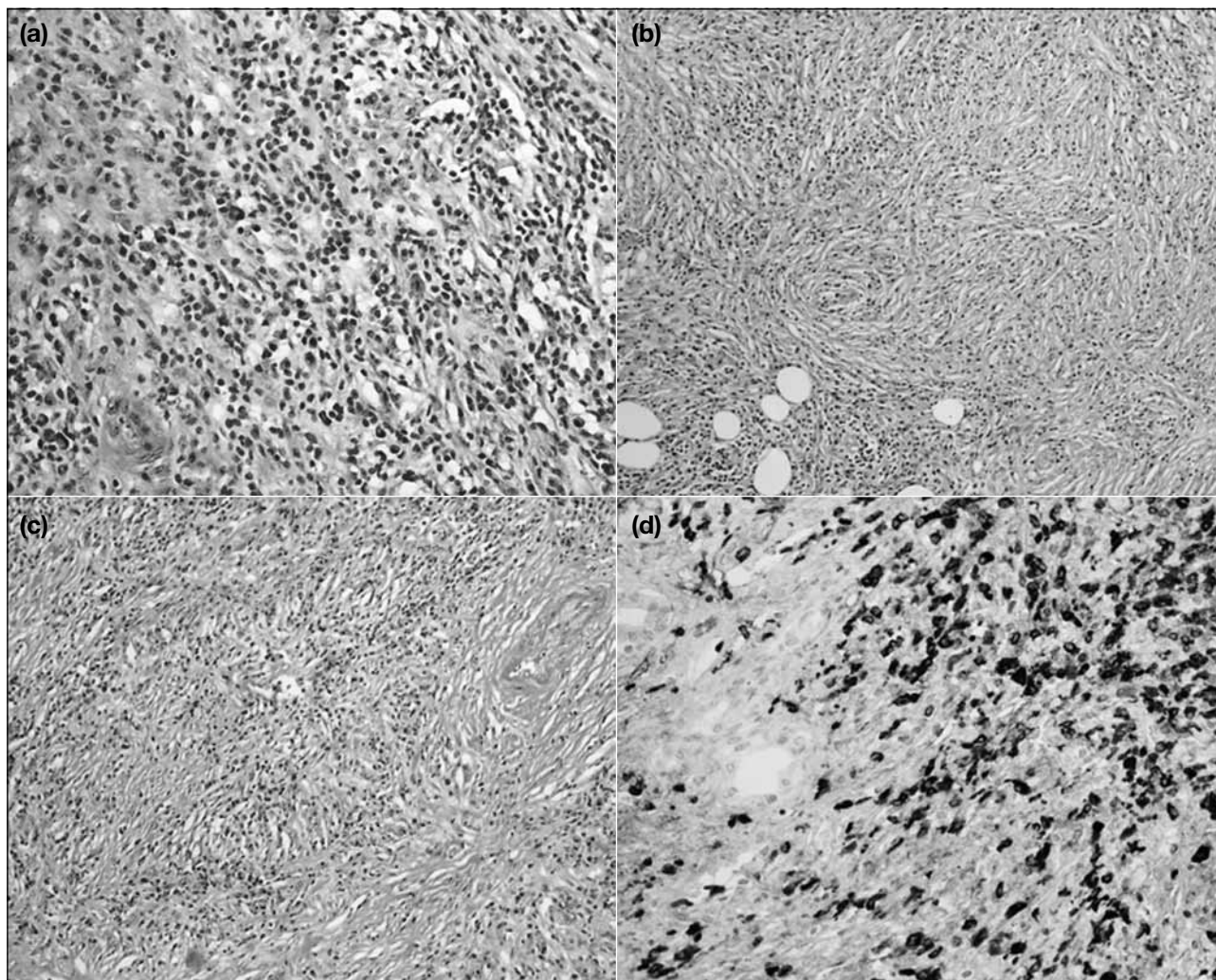
AIP was diagnosed only following surgery in eight

**Table.** Pancreatic parenchymal imaging findings.

Radiological features	No. (%) of subjects
Diffuse swelling of pancreas	4 (31)
Focal pancreatic mass	6 (46)
Segmental swelling of pancreas	3 (23)
Capsule-like rim	2 (15)
Peri-pancreatic fat stranding	0
Pancreatic calcification	0
Pancreatic pseudocyst	0
Narrowing of intra-pancreatic common bile duct	11 (85)



**Figure 4.** Typical extrapancreatic manifestations of autoimmune pancreatitis (AIP). (a) Stricture of lower common bile duct (curved arrow) with upstream dilatation of biliary tree. If pancreatic parenchymal findings are subtle, it can be misdiagnosed as cholangiocarcinoma. (b) Bilateral multifocal wedge-shaped hypo-enhancing lesions (arrows), typical of renal involvement of AIP. (c) Para-aortic soft tissue lesion encasing aorta and inferior vena cava (arrowheads), with medial deviation of bilateral ureters (not shown in this image), classical of retroperitoneal fibrosis.



**Figure 5.** Classic pathological features of autoimmune pancreatitis. (a) Dense lymphoplasmacytic infiltration (H&E; original magnification, x 200). (b) Dense interstitial storiform fibrosis (H&E; original magnification, x 100). (c) Obliterative phlebitis (H&E; original magnification, x 100). (d) Immunostaining for immunoglobulin G4 shows abundant positive plasma cells (original magnification, x 200).

patients. Parenchymal imaging revealed either atypical or intermediate imaging findings in all cases. None of them had serum IgG4 level checked preoperatively. Nonetheless serum IgG4 was measured in seven subjects soon after operation when the diagnosis of AIP was made; the level was elevated in all cases (mean, 647 mg/dl). Extrapancreatic manifestations were present in two cases — one with renal involvement and the other with salivary gland enlargement. None of them underwent endoscopic ultrasound-guided biopsy (EUS-Bx), endoscopic retrograde pancreatography, or steroid trial.

## DISCUSSION

AIP is an increasingly recognised form of chronic

pancreatitis, characterised by its autoimmune manifestations in clinical, radiological, histological, and laboratory tests. AIP patients in our series showed similar but not identical features to other Asian populations.<sup>6</sup> When compared with patients in Japan/Korea and China/Taiwan, our patients appeared to have a higher male-to-female ratio (our study vs. Japan + Korea vs. China + Taiwan: 5.5:1 vs. 3.2:1 vs. 8:1), more symptoms of obstructive jaundice (69% vs. 49.4% vs. 73.6%), more epigastric discomfort (54% vs. 23.5% vs. 26.4%), more weight loss (46% vs. 18% vs. 47.2%), were less likely to be asymptomatic (7.7% vs. 16.5% vs. 11.1%), more extrapancreatic manifestations, higher prevalence (100% vs. 73.6% vs. 100%) and mean level (1627 mg/dl vs. 442.8 mg/dl vs. 729.3 mg/dl)

of elevated serum IgG4, and more atypical and intermediate imaging findings (69.2% vs. 28.2% vs. 70.8%). Surprisingly, our data are very similar to those of China and Taiwan.<sup>6</sup> Is there a genuine difference in manifestations in different geographical locations, or is it related to the small sample size of available data? A further large-scale, multicentre cohort study should be performed to answer this question.

It is not an easy task to differentiate AIP from other forms of chronic pancreatitis and pancreatic cancer solely by clinical examination. Imaging examinations are therefore usually requested. AIP can manifest radiologically in classic cases as diffuse swelling of the pancreas with a featureless border. Radiologists should be able to make the diagnosis or raise the suspicion of AIP in such cases. An absence of significant peri-pancreatic fat stranding allows us to differentiate it from acute pancreatitis that also typically manifests as diffuse pancreatic swelling. Presence of 'capsule-like rim' is a strong indicator of AIP rather than pancreatic cancer. AIP can also manifest as a focal pancreatic mass and segmental swelling of the pancreas: radiologists are less helpful in such cases as there are no definite radiological findings to differentiate between focal AIP and pancreatic adenocarcinoma without distant metastasis. Presence of extrapancreatic manifestations such as retroperitoneal fibrosis, renal involvement, proximal bile duct stricture, and salivary gland enlargement may have a role.<sup>7,8</sup> Serology, pancreatic ductal imaging, histology, and steroid trial would be helpful in this scenario.

Subgroup analysis of AIP patients diagnosed only after surgery shows none of them could have been diagnosed preoperatively according to ICDC.<sup>9</sup> Nonetheless, a marked elevation in serum IgG4 level after operation allows us to assume at least similar, if not higher, readings preoperatively. Positive histology results of surgical specimens also infer positive histology if EUS-Bx had been performed preoperatively. Therefore, we can conclude that most, if not all, cases could have been diagnosed as AIP preoperatively if serum IgG4 level had been measured and EUS-Bx performed, and major surgery such as Whipple's procedure could be avoided. Does this mean we have to send all patients with focal pancreatic mass or segmental swelling of the pancreas for EUS-Bx? The answer is negative. First, AIP is a rare disease compared with pancreatic cancer. Second, EUS-Bx is technically demanding. Last but not the least, the procedural risk of EUS-Bx, although small, is another concern. Balancing the risks and benefits, we propose

that serum IgG4 should be checked in all patients with radiologically suspected pancreatic and extrahepatic biliary malignancy at a pancreatic level in the absence of definite distant metastasis, i.e. focal pancreatic mass or lower common bile duct stricture. Typical extra-pancreatic manifestations of AIP, such as retroperitoneal fibrosis, renal involvement, proximal bile duct stricture, and salivary gland enlargement should also be looked for. Elevation of serum IgG4, especially when higher than double of the normal upper limit,<sup>7</sup> and presence of extrapancreatic manifestations should raise the possibility of AIP. Cautious use of EUS-Bx, endoscopic retrograde pancreatography, and steroid trial depending on clinical suspicion would be helpful to exclude malignancy and confirm diagnosis of AIP.

A limitation of this study was the small sample size. This is attributed partly to the rarity of the disease. Lack of standardised diagnostic criteria, inadequate experience of gastroenterologists, surgeons, radiologists, and pathologists to this new disease entity also play a role. Development of the ICDC in 2011 and accumulation of knowledge about AIP in recent decades have corrected these shortfalls.

## CONCLUSIONS

In our series, AIP manifested similarly to cases in China and Taiwan but differed to those in Japan and Korea. This raises a suspicion of different manifestations of AIP in different geographical locations. A further large-scale multicentre cohort study would be helpful to answer this question. AIP is well known to mimic pancreatic and biliary malignancies; radiologists should be familiar with the typical imaging findings of AIP. We propose that serum IgG4 is measured and extrapancreatic manifestations looked for in cases of radiologically suspected pancreatic and extrahepatic biliary malignancy at a pancreatic level in the absence of definite distant metastasis. Cautious use of EUS-Bx, endoscopic retrograde pancreatography, and steroid trial in selected cases depending on clinical suspicion would be valuable. Some Whipple's procedures can hopefully be avoided by these measures.

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