Digestive Surgery

Research Article

Dig Surg 2022;39:32–41
DOI: 10.1159/000521490

Received: September 1, 2021
Accepted: November 28, 2021
Published online: December 15, 2021

Surgery in Autoimmune Pancreatitis

Sara Nikolic[a, b] Poya Ghorbani[c, d] Raffaella Pozzi Mucelli[c, e] Sam Ghazi[f]
Francisco Baldaque-Silva[a, d] Marco Del Chiaro[c, d, g] Ernesto Sparrelid[c, d]
Caroline S. Verbeke[f, h] J.-Matthias Löhr[c, d] Miroslav Vujasinovic[a, d]

[a]Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden; [b]Department of Gastroenterology, Clinic for Internal Medicine, University Medical Centre Maribor, Maribor, Slovenia; [c]Department of Clinical Science, Intervention, and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden; [d]Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden; [e]Department of Abdominal Radiology, Karolinska University Hospital, Stockholm, Sweden; [f]Department of Pathology, Karolinska University Hospital, Stockholm, Sweden; [g]Division of Surgical Oncology, Department of Surgery, University of Colorado, Anschutz Medical Campus, Aurora, CO, USA; [h]Department of Pathology, Oslo University Hospital, Oslo, and University of Oslo, Oslo, Norway

Keywords
Autoimmune pancreatitis · IgG4 · Pancreatic cancer · Surgery

Abstract
Introduction: Autoimmune pancreatitis (AIP) is a disease that may mimic malignant pancreatic lesions both in terms of symptomatology and imaging appearance. The aim of the present study is to analyze experiences of surgery in patients with AIP in one of the largest European cohorts. ***Patients and Methods:*** We performed a single-center retrospective study of patients diagnosed with AIP at the Department of Abdominal Diseases at Karolinska University Hospital in Stockholm, Sweden, between January 2001 and October 2020. ***Results:*** There were 159 patients diagnosed with AIP, and among them, 35 (22.0%) patients had surgery: 20 (57.1%) males and 15 (42.9%) females; median age at surgery was 59 years (range 37–81). Median follow-up period after surgery was 50 months (range 1–235). AIP type 1 was diagnosed in 28 (80%) patients and AIP type 2 in 7 (20%) patients. Malignant and premalignant lesions were diagnosed in 8 (22.9%) patients for whom AIP was not the primary differential diagnosis, but in all cases, it was described as a simultaneous finding and recorded in retrospective analysis in histological reports of surgical specimens. ***Conclusions:*** Diagnosis of AIP is not always straightforward, and in some cases, it is not easy to differentiate it from the malignancy. Surgery is generally not indicated for AIP but might be considered in patients when suspicion of malignant/premalignant lesions cannot be excluded after complete diagnostic workup.

Introduction

Autoimmune pancreatitis (AIP) is a distinct form of pancreatitis characterized clinically by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate

Marco Del Chiaro and Caroline S. Verbeke: current affiliation of the authors previously employed at Karolinska University Hospital.
J.-Matthias Löhr and Miroslav Vujasinovic contributed equally.

karger@karger.com
www.karger.com/dsu

Correspondence to:
Miroslav Vujasinovic, miroslav.vujasinovic@sll.se

Table 1. Demographic and clinical features of patients who underwent surgery

	Total (*N* = 35)	AIP 1 (*N* = 28) (80%)	AIP 2 (*N* = 7) (20%)
Male, *n* (%)	20 (57.1)	17 (85.0)	3 (15.0)
Female, *n* (%)	15 (42.9)	11 (73.3)	4 (26.7)
Age at AIP diagnosis (median, min–max)	59 (37–81)	60 (41–81)	57 (37–75)
Follow-up (median, min–max), months	50 (1–235)	66 (1–235)	24 (1–109)
Alcohol consumption >5 U, *n* (%)	4 (12.5)	4 (100.0)	0
Smoker, *n* (%)			
Former	7 (22.6)	5 (71.4)	2 (28.6)
Active	2 (6.5)	2 (100.0)	0
Symptoms at diagnosis, *n* (%)			
Abdominal pain	17 (48.6)	15 (88.2)	2 (11.8)
Weight loss[1]	17 (48.6)	16 (94.1)	1 (5.9)
Jaundice	15 (42.9)	14 (93.3)	1 (6.7)
Acute pancreatitis	5 (14.3)	3 (60.0)	2 (40.0)
New-onset diabetes	3 (8.6)	2 (66.7)	1 (33.3)
Incidental finding[2]	4 (11.4)	1 (25.0)	3 (75.0)

N, patient number; AIP, autoimmune pancreatitis. [1] Fisher exact test showed tendency to statistically significant difference with $p = 0.088$. [2] Fisher exact test showed a statistically significant difference with $p = 0.019$.

and fibrosis, and therapeutically by a dramatic response to glucocorticoids (GC) [1]. It is a special form of chronic pancreatitis with 2 histopathologically distinct subtypes: lymphoplasmacytic sclerosing pancreatitis (AIP type 1) and idiopathic duct-centric pancreatitis (AIP type 2) [2]. AIP type 1 is characterized by a presence of IgG4 [3], represents pancreatic involvement in a larger group of IgG4-related diseases, and is commonly associated with other organ involvement (OOI), especially immune-related cholangitis, sialadenitis, dacryoadenitis, kidney involvement [4], lung involvement, and vasculitis [5]. AIP type 2 is not associated with IgG4, and approximately 30% of reported cases have associated inflammatory bowel disease [1]. According to the International Consensus Diagnostic Criteria (ICDC), the diagnosis of AIP is based on the presence of one or more of the following factors: pancreatic parenchyma and pancreatic duct imaging, serum IgG4 level (for AIP type 1), OOI, histology of the pancreas, and response to GC treatment [1]. However, diagnosis of AIP is not always straightforward, and in some cases, it is not easy to differentiate it from pancreatic cancer. In 2014, the International Study Group of Pancreatic Surgery reported that 5–13% of patients undergoing surgical resections due to suspected malignancy had benign findings on pathology, with AIP accounting for 30–43% of these findings [6]. IgG4-related disease, and particularly AIP, may be associated with an increased risk of developing malignant disease compared with the general population; therefore, life-long surveillance in patients with IgG4-related disease is advised [3, 7]. Surgery is generally not indicated for AIP, but it might be considered in patients when suspicion of pancreatic cancer cannot be excluded after complete diagnostic workup. The aim of the present study was to analyze the impact of surgery in patients with suspicious pancreas malignancy and whom were given a final diagnosis of AIP.

Patients and Methods

We performed a single-center retrospective study in patients diagnosed with AIP between January 2001 and October 2020. Diagnosis of AIP was confirmed according to ICDC criteria published in 2011 [1] (retrospective analysis and diagnosis according to ICDC criteria were performed for patients diagnosed during the period before the publication of ICDC). Our cohort consists of 159 patients for whom some demographic and clinical characteristics were already described in earlier publications of our group [4, 5, 8, 9]. All patients with clinically suspected AIP were discussed at multidisciplinary pancreas meetings which are held twice a week. Indication for surgery was only reserved for those patients with a solid focal pancreatic mass for whom it was not possible to rule out cancer or where cancer was highly suspicious.

Results

Patients

There were 159 patients with AIP, and among them, 35 (22.0%) patients had surgery: 20 (57.1%) males and 15 (42.9%) females; median age at surgery was 59 years

Table 2. Demographic and clinical features of patients who underwent surgery due to the suspected pancreatic mass where it was not possible to exclude cancer (autoimmune pancreatitis was found on histopathological analysis)

No.	Gender	Age (at surgery)	Clinical features	Year	Surgery	PHD	Relapse
1	Female	53	Symptoms: abdominal pain, weight loss CT: negative MRI (2 months later): suspected mass in the tail of pancreas CA 19-9: NA	2001	Distal pancreatectomy + splenectomy Postop complications: no	AIP type 1	Relapses after surgery (2×) First relapse treated with GC During second relapse, surgery was performed (2013) due to suspected cholangiocarcinoma (extended right hepatectomy) and PHD showed autoimmune cholangitis Status at last contact: recurrent cholangitis (clinically and radiologically) due to obstruction in the entero-enteroanastomosis and reflux up to the biliary limb
2	Male	75	Symptoms: abdominal pain, weight loss, jaundice, new-onset diabetes CT: dilatation of bile ducts and main pancreatic duct EUS: suspected mass in head of pancreas (FNB inconclusive) ERCP: choledochal stricture (benign brush cytology) *CA 19-9: 77	2012	Surgery 2×: pancreatoduodenectomy (2012) and completion pancreatectomy + splenectomy (2014) Postop complications: no	AIP type 1	Relapses of IgG4-related disease even after pancreas surgeries, in form of OOI (aorta, kidneys, bile ducts, retroperitoneal fibrosis, dacryoadenitis) Treatment with rituximab during 2019 that stopped due to risk associated with COVID, currently low-dose GC (5 mg prednisone), in clinical remission
3	Male	79	Symptoms: jaundice CT: suspected mass/stricture in distal bile duct ERCP: choledochal stricture (benign brush cytology) CA 19-9: 12	2012	Intraoperatively decided as nonresectable; double bypass was performed Postop complications: no	AIP type 1	Relapse after surgery, treated with GC in total 20 months (maintained 5 mg prednisone); thereafter complete clinically and radiologically remission without ongoing treatment
4	Female	68	Symptoms: jaundice, weight loss CT: chronic pancreatitis MRI: suspected mass in head of pancreas CA 19-9: NA	2004	Pancreatoduodenectomy Postop complications: no	AIP type 1 and IgG4-related cholangitis	Patient died 7 years after surgery (cause of death unknown)
5	Male	37	Symptoms: weight loss, jaundice, new-onset diabetes US: suspected mass in head of pancreas CT: dilated bile ducts ERCP: choledochal stricture (brush cytology NA) CA 19-9: 54	2013	Pancreatoduodenectomy (the patient had pancreas anomaly in form of aplasia of body and tail thus resulting in total pancreatectomy) Postop complications: no	AIP type 2	No signs of OOI
6	Male	49	Symptoms: abdominal pain, jaundice CT: perihilar biliary stricture suspicious for perihilar cholangiocarcinoma CA 19-9: NA	2015	Pancreatoduodenectomy Postop complications: no	AIP type 1	Relapse after surgery (ongoing), candidate for GC or RTX
7	Male	70	Symptoms: weight loss, jaundice CT, MRI, and ERCP: perihilar biliary stricture, suspicion of perihilar cholangiocarcinoma (benign brush cytology) CA 19-9: NA	2012	Extended right hepatectomy + segment 1 and extrahepatic bile ducts Postop complications: patient died 7 months after diagnosis due to multiorgan failure	AIP type 1 and IgG4-related cholangitis	Patient died 7 months after diagnosis due to multiorgan failure (cholangitis, sepsis, liver failure, encephalopathy)
8	Female	49	Symptoms: weight loss, jaundice US and CT: suspected mass in the head of pancreas and dilated bile ducts CA 19-9: NA	2010	Intraoperatively decided as nonresectable; double bypass was performed Postop complications: no	AIP type 1	Relapse 1× after surgery, treated with GC, thereafter complete clinically and radiologically remission
9	Female	57	Symptoms: jaundice CT/MRI (2009): NA CT and MRI (2013): bile duct stricture in right liver lobe CA 19-9: NA	2009	Surgery 2×: laparotomy and pancreas biopsy due to suspected pancreas cancer (2009) and right hepatectomy due to suspected intrahepatic cholangiocarcinoma (2013) Postop complications: no	AIP type 1	Postoperative complications (abscess) Relapse 5× after surgery; treated with GC, cyclosporine, and mycophenolate mofetil Clinically and radiologically complete remission on low-dose GC treatment (5 mg prednisolone)
10	Female	47	Symptoms: abdominal pain CT, MRI, and ERCP: stricture in intrapancreatic common bile duct (benign brush cytology) CA 19-9: 7	2010	Pancreatoduodenectomy Postop complications: no	AIP type 1	No relapse after surgery Clinically and radiologically complete remission without ongoing treatment

Table 2 (continued)

No.	Gender	Age (at surgery)	Clinical features	Year	Surgery	PHD	Relapse
11	Male	75	Symptoms: acute pancreatitis CT and MRI: stricture in main pancreatic duct CA 19-9: 5	2017	Central pancreas resection Postop complications: no	AIP type 2	No relapse after surgery
12	Female	53	Symptoms: acute pancreatitis CT: suspected mass in tail of pancreas CA 19-9: 12	2017	Distal pancreatectomy + splenectomy + resection of left colonic flexure Postop complications: no	AIP type 1	Relapse after surgery in form of IgG4-related orbit involvement, currently under treatment with rituximab
13	Male	69	Symptoms: abdominal pain, weight loss CT and MRI: suspected mass in head of pancreas and distal common bile duct stricture CA 19-9: 15	2014	Pancreatoduodenectomy and portal vein reconstruction Postop complications: no	AIP type 1	No relapse after surgery
14	Male	68	Symptoms: jaundice, new-onset diabetes CT/MRI: suspected mass in head of pancreas and distal common bile duct stricture CA 19-9: NA	2015	Pancreatoduodenectomy Postop complications: no	AIP type 1	No relapse after surgery
15	Male	70	Symptoms: weight loss, jaundice, loss of appetite CT: suspected mass in head of pancreas and stricture in common bile duct MRI and ERCP: distal bile duct stricture (benign brush cytology) CA 19-9: 14	2017	Initially planned pancreatoduodenectomy that was converted to total pancreatectomy + splenectomy intraoperatively Postop complications: 1. Stricture in hepaticojejunostomy treated with PTC and internal drainage 2. Leakage from gastroenteroanastomosis with formation of cutaneous fistula	AIP type 1	No relapses of IgG4-related disease after surgery
16	Male	81	Symptoms: weight loss, jaundice, new-onset diabetes US, CT, MRI, and ERCP: distal common bile duct stricture (benign brush cytology) EUS: small lesion in the head of pancreas (benign FNA) CA 19-9: NA	2007	Pancreatoduodenectomy Postop complications: no	AIP type 1	No relapse after surgery
17	Male	65	Symptoms: jaundice CT, MR, and ERCP: perihilar biliary stricture, suspicious for perihilar cholangiocarcinoma (benign brush cytology) CA 19-9: 5	2017	Extended right hepatectomy + segment 1 and extrahepatic bile ducts Postop complications: 1. Wound rupture – reoperated 1× 2. Percutaneous drainage of fluid collections in abdomen 1× and in pleura 1× + IV antibiotics 3. Bilateral deep vein thrombosis	IgG4-related cholangitis	Relapse of IgG4-related diseases (AIP type 1 with sialadenitis and lung involvement), currently treated with rituximab
18	Male	41	Symptoms: abdominal pain, acute pancreatitis; weight loss CT: suspected mass in head of pancreas MRI: distal common bile duct stricture CA 19-9: 11	2019	Pancreatoduodenectomy Postop complications: 1. Intra-abdominal fluid collections, drainage not possible, treated with IV antibiotics 2. Wound rupture – reoperated 2×	AIP type 1	No relapse after surgery
19	Female	69	Symptoms: weight loss, jaundice CT, MRI, and ERCP: distal common bile duct stricture (benign brush cytology) CA 19-9: 149	2013	Pancreaticoduodenectomy Postop complications: no	AIP type 1	No relapse after surgery
20	Male	65	Symptoms: weight loss, diarrhea CT: suspected mass in tail of pancreas CA 19-9: 16	2020	Distal pancreatectomy + splenectomy Postop complications: no	AIP type 1	No relapse after surgery
21	Male	67	Symptoms: weight loss, abdominal pain CT/MRI: suspected mass in head of pancreas CA 19-9: NA	2017	Pancreatoduodenectomy Postop complications: no	AIP type 1 and IgG4-related cholangitis	Relapse after surgery, treated with GC
22	Male	65	Symptoms: jaundice, abdominal pain US, CT, MRI, and ERCP: distal bile duct stricture (benign brush cytology) CA 19-9: 87	2008	Pancreatoduodenectomy Postop complications: no	AIP type 1	No relapse after surgery

Table 2 (continued)

No.	Gender	Age (at surgery)	Clinical features	Year	Surgery	PHD	Relapse
23	Female	57	Symptoms: jaundice, weight loss CT: suspected mass in head of pancreas CA 19-9: 7	2011	Initially planned pancreatoduodenectomy that was converted to total pancreatectomy and splenectomy intraoperatively Postop complications: Infection of unknown origin, treated with IV antibiotics	AIP type 1	No relapse after surgery; patient died 17 months after surgery due to pneumonia and sepsis
24	Female	56	Symptoms: history of disseminated malignant melanoma with good response on oncological treatment (incidental pancreatic finding during the follow-up) CT, PET, and MRI: suspected mass in head of pancreas EUS: no pathology CA 19-9: 7	2020	Pancreatoduodenectomy Postop complications: no	AIP type 2	No relapse after surgery
25	Female	56	Symptoms: abdominal pain MRI: suspected mass in head of pancreas CA 19-9: 5	2011	Pancreatoduodenectomy and total gastrectomy (total gastrectomy was performed due to technical reasons because the patient had previous history of vertical banded gastroplasty for weight control) Postop complications: 1. Respiratory insufficiency 2. Bile leakage (from hepaticojejunostomy) causing septicemia – reoperation postoperative day 5 3. Percutaneous drainage of fluid collection in abdomen 1× and in pleura 1× + IV antibiotics 4. Lung embolism	AIP type 1	No relapse after surgery; patient died 7 years after surgery due to pneumonia and sepsis
26	Male	62	Symptoms: vomiting, jaundice CT: duodenal obstruction and distal bile duct stricture CA 19-9: 29	2008	Double bypass Postop complications: no	AIP type 1	No relapse after surgery (treated due to autoimmune rheumatological disease)
27	Male	49	Symptoms: none (patient was followed due to IPMN found 2 years before imaging was performed due to IBD) MRI: multifocal side-branch IPMN with worrisome features CA 19-9: 21	2020	Total pancreatectomy and splenectomy Postop complications: no	Pseudocyst and AIP type 1	No relapse after surgery

No., patient number; CT, computed tomography; MRI, magnetic resonance imaging; FNA, fine-needle aspiration; FNB, fine-needle biopsy; GC, glucocorticoids; AIP, autoimmune pancreatitis; IgG4, immunoglobulin G4; MCN, mucinous cystic neoplasm with high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; HGD, high-grade dysplasia; LGD, low-grade dysplasia; PDAC, pancreatic ductal adenocarcinoma; PET, positron emission tomography; COVID, coronavirus disease; ERCP, endoscopic retrograde cholangiopancreatography; US, ultrasound; EUS, endoscopic ultrasound; NA, not available; IBD, inflammatory bowel disease; OOI, other organ involvement; IV, intravenous. *Reference values for CA 19-9: <37 kE/L.

(range 37–81). Median follow-up period after surgery was 50 months (range 1–235). Demographic and clinical features of patients are presented in Table 1.

Surgery

Types of surgical procedures and surgery-related complications are presented in Tables 2 and 3. AIP type 1 was diagnosed in 28 (80%) patients and AIP type 2 in 7 (20%) patients. Malignant and premalignant lesions were diagnosed in 8 (22.9%) patients (for whom AIP was not the primary differential diagnosis, but in all cases, it was described as a simultaneous finding and recorded in retrospective analysis in histological reports of surgical specimens). Pancreatic ductal adenocarcinoma (PDAC) was diagnosed in 2 (5.7%) patients (both with AIP type 1). Other pancreatic lesions were diagnosed in 6 (17.1%) patients (2 patients with AIP type 1 and 4 patients with AIP type 2): mucinous cystic neoplasm with high-grade dysplasia (MCN HGD) in 1; mucinous cystic neoplasm with low-grade dysplasia (MCN LGD) in 1; intraductal papillary mucinous neoplasm with high-grade dysplasia (IPMN HGD) in 1, and intraductal papillary mucinous neoplasm with low-grade dysplasia (IPMN LGD) in 3 patients. In this subgroup of patients, surgery was per-

Table 3. Demographic and clinical features of patients who underwent surgery due to pancreatic cystic lesions with worrisome features (autoimmune pancreatitis was an incidental finding on histopathological analysis)

1	Female	42	Symptoms: pain CT: locally advanced tumor in tail of pancreas, suspicion of malignified MCN CA 19-9: 19	2017	Multivisceral resection: Distal pancreatectomy Splenectomy Left-sided nephrectomy Subtotal colectomy Duodenal resection Portal vein reconstruction Postop complications: 1. Postoperative pancreatic fistula grade B; treated with sphincterotomy and main pancreatic duct stenting for downstream control 2. Percutaneous drainage of fluid collection in abdomen 3× and in pleura 1× + IV antibiotics 3. Transduodenal drainage of fluid collection 1×	MCN HGD and AIP type 1	No relapse after surgery
2	Female	67	Symptoms: none (incidental finding during the workup of chronic cough and CT-thorax was performed first) CT: suspected mass in tail of pancreas CA 19-9: 28	2018	Distal pancreatectomy + splenectomy Postop complications: none	Mixed type IPMN LGD and AIP type 2	No relapse after surgery
3	Female	44	Symptoms: clinically asymptomatic. elevated liver function test on routine checkup CT and MRI: suspected mass in tail of pancreas CA 19-9: 34	2018	Laparoscopic distal pancreatectomy + splenectomy Postop complications: none	IPMN LGD and AIP type 2	No relapse after surgery
4	Male	59	Symptoms: abdominal pain, recurrent acute pancreatitis CT and MRI: mixed type IPMN in head of pancreas CA 19-9: 9	2016	Pancreatoduodenectomy Postop complications: none	Mixed type IPMN LGD and AIP type 1	MR signs of cholangitis in clinically asymptomatic patient with normal laboratory results in biochemistry and IgG4
5	Male	47	Symptoms: abdominal pain and acute pancreatitis CT and MRI: cystic lesion in tail of pancreas CA 19-9: 4	2018	Distal pancreatectomy and splenectomy Postop complications: none	Mixed type IPMN HGD and AIP	No relapse after surgery
6	Female	44	Symptoms: abdominal pain CT: suspected mass in head of pancreas CA 19-9: NA	2008	Pancreatoduodenectomy Postop complications: 1. Reoperation postoperative day 3 due to retroperitoneal hemorrhage, source not identified 2. Percutaneous drainage of fluid collection in abdomen 1× + IV antibiotics	PDAC = T3N1Mx, R0 resection, and AIP type 1	Patient died of PDAC 14 months after surgery
7	Female	47	Symptoms: abdominal pain CT: cystic tumor in tail of pancreas CA 19-9: 24	2012	Distal pancreatectomy with splenectomy and portal vein reconstruction Postop complications: none	MCN with HGD and transition into poorly differentiated PDAC pT2N0, R0 resection, and AIP type 1	No relapse after surgery
8	Female	64	Symptoms: abdominal pain CT, MR, EUS, ERCP: cystic tumor in tail of pancreas, suspicion of IPMN CA 19-9: 42	2011	Distal pancreatectomy and splenectomy Postop complications: none	MCN LGD and AIP type 2	No relapse after surgery

CT, computed tomography; MRI, magnetic resonance imaging; FNA, fine-needle aspiration; FNB, fine-needle biopsy; GC, glucocorticoids; AIP, autoimmune pancreatitis; IgG4, immunoglobulin G4; MCN, mucinous cystic neoplasm with high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; HGD, high-grade dysplasia; LGD, low-grade dysplasia; PDAC, pancreatic ductal adenocarcinoma; PET, positron emission tomography; COVID, coronavirus disease; ERCP, endoscopic retrograde cholangiopancreatography; US, ultrasound; EUS, endoscopic ultrasound; NA, not available; IBD, inflammatory bowel disease; OOI, other organ involvement; IV, intravenous. *Reference values for CA 19-9: <37 kE/L.

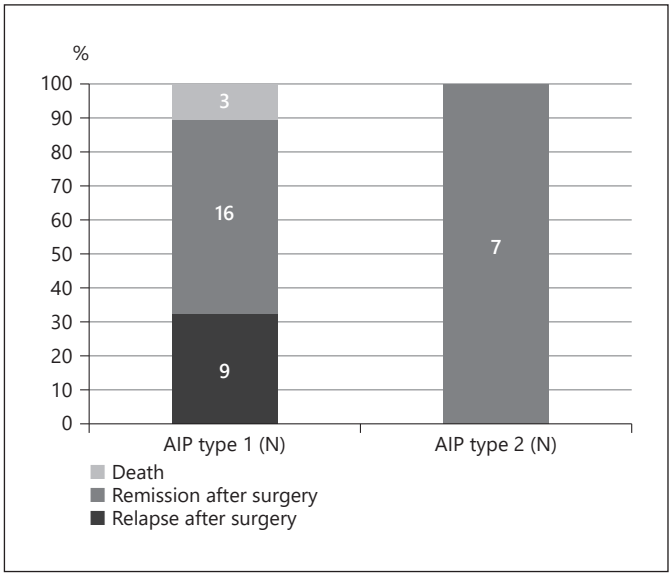

Fig. 1. Clinical status of AIP patients after surgery. N, patient number; AIP, autoimmune pancreatitis.

formed due to initially suspected pancreatic cancer or pancreatic cyst with worrisome features after presentation on multidisciplinary meetings (Table 3).

Serum Levels of CA 19-9 before Surgery

Data on CA 19-9 levels were available for 20 (57.1%) patients. In 15 of 20 patients (75%), CA 19-9 was normal and in 5 (25%) elevated.

Data on CA 19-9 levels were available for 7 of 8 patients with pancreatic lesions and was slightly elevated (42 kE/L) in only 1 patient (MCN LGD) and normal in other 6 patients (PDAC 1×; IPMN HGD 1×; IPMN LGD 3×; MCN HGD 1×).

Serum Levels of IgG4 in Patients with Histologically Confirmed Autoimmune Pancreatitis Type 1

Data on IgG4 serum levels were available for 20 patients with AIP type 1 at the time of diagnosis: in 7 (35%) of 20 patients, IgG4 levels were elevated, and in 13 (65%) patients, IgG4 levels were normal. In only 1 patient, IgG4 levels were >3× over upper limits of normal.

Data on IgG4 serum levels at the time of surgery and at the last control with patients were known in 13 patients with AIP type 1: (a) elevated values at diagnosis and after surgery were present in 5 patients; (b) normal values at diagnosis and after surgery were present in 5 patients; (c) in 2 patients, initial normal values were converted to elevated values at the last control; and (d) only 1 patient's initially elevated IgG4 values normalized after the surgery.

Clinical Status of AIP at the Time of Data Analysis

Patients with AIP type 1: 3 patients died (one of PDAC, one 7 months after surgery due to postoperative complications, and one 7 years after surgery – cause of death was not available from the medical records); 16 (57.1%) patients had no relapse of AIP after surgery. Relapse after surgery was diagnosed in 9 patients. Time period to relapse for the 9 AIP type 1 patients was 0–10 years. Immediate relapse after surgery was noted in 5 (55.6%) patients; 1 patient had relapse 6 months after surgery; 2 patients had relapse 3 years after surgery, and one 10 years after surgery. Four patients are currently in clinical remission (receiving treatment), and 5 patients had relapse treated with GC and rituximab (Table 2; Fig. 1).

Patients with AIP type 2: no relapses after surgery were noted – Table 2 and Figure 1. OOI was present in 25 (71.4%) patients with AIP: immune-related cholangitis in 19; inflammatory bowel disease in 6; kidney involvement in 5; lung involvement in 3; vasculitis in 2; duodenal papilla in 1; sialadenitis in 1; orbit involvement in 1.

Postoperative Complications

Six out of 35 (17%) patients had major complications (defined as Clavien-Dindo >II). Among them, 1 had a serious complication (death = Clavien-Dindo V); 1 was admitted to intensive care (Clavien-Dindo IV), and 4 underwent intervention under full anesthesia (Clavien-Dindo IIIb).

Discussion

Surgery was performed in 22% of patients with AIP in our historical cohort, and the number of operated patients did not decline over time (Fig. 2), despite increasing knowledge in AIP and overall technical improvement in the field of cross-sectional imaging and endoscopy.

In approximately 23% of patients, malignant or premalignant lesions were present simultaneously with AIP, and in all cases, it was found in retrospective analysis of medical/pathological records. It is of importance to emphasize that in this subgroup of patients, AIP was not the primary differential diagnosis, but it was found as a simultaneous pathology in patients with suspected pancreatic lesions.

Unfortunately, serum levels of IgG4 were not helpful in differential diagnosis between AIP type 1 and malig-

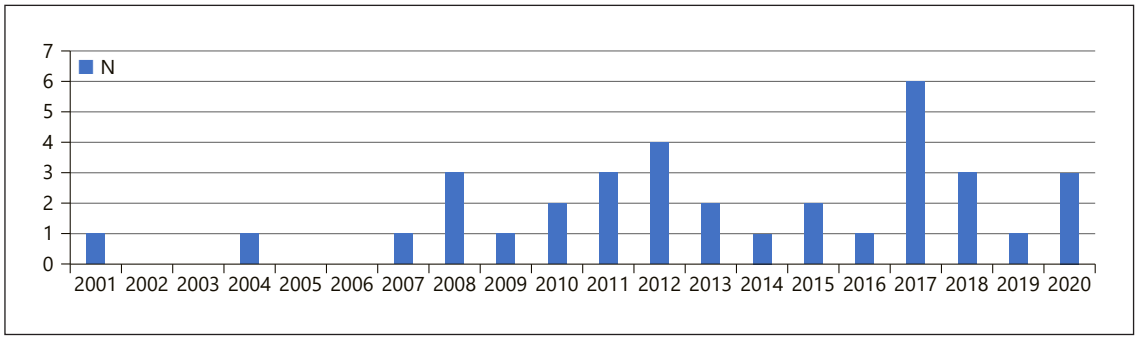

Fig. 2. Number of patients undergoing surgery per year.

nant lesions as it was elevated in only 35% of patients in whom AIP type 1 was pathologically confirmed after the surgery. Several study groups have reported a lack of sensitivity and specificity of the IgG4 serum level to establish the diagnosis of IgG4-related disease or to distinguish it from other diseases [3, 10–12], emphasizing its diagnostic value only when the level is higher than 4 times the upper limit of normal, which is unfortunately the case in only a minority of patients [3]. Even elevated serum CA 19-9 levels are influenced by factors, such as cholangitis, and when used alone, CA 19-9 displays limited accuracy in differentiating AIP from PDAC, that was the case also in our study, since CA 19-9 was normal in 6 of 7 patients with pancreatic lesions [3]. Differentiation between AIP type 2 and pancreatic malignancy is even more challenging as we have no reliable biochemical markers of AIP type 2. Endoscopic ultrasound (EUS) provides pancreatic imaging findings suggestive of AIP and is widely used for obtaining tissue samples for the histological diagnosis of the disease [3]. However, in clinical practice, tissue obtained by EUS fine-needle biopsy may not be representative, decreasing its diagnostic yield. A recently published meta-analysis, which was based on 20 studies with rigid inclusion criteria, revealed that IgG4 immunostaining of pancreatic, biliary, and ampullary tissue can be useful for supporting a diagnosis of AIP, with a sensitivity of 64% and a specificity of 93% [13]. Authors concluded that a biopsy showing little or no evidence of AIP cannot be used alone to exclude this diagnosis, unless a positive alternative diagnosis can be made [14, 15]. The consensus statement on the pathology of IgG4-related disease recommends counting "3" high-powered fields (HPFs) with the highest number of IgG4-positive plasma cells ("hotspots") and calculating the average number of IgG4-positive cells within those fields [16]. It is obvious that random field counting might result in an underestimation of IgG4-positive cells, especially due to patchy cell-distribution in IgG4-related disease [16]. The consensus statement on the pathology of IgG4-related disease separately stipulates a cutoff of 50 IgG4-positive cells/HPF in resection specimens and 10 cells/HPF in biopsy specimens [16], whereas the ICDC provide a unified cutoff of 10 cells/HPF [1]. The studies included in a meta-analysis indicated that more research groups used a cutoff value of 10 IgG4-positive cells/HPF even in surgical specimens [13]. It is important to be careful in analysis and interpretation of all cases with precancerous/cancerous lesions and incidental AIP findings (8 patients in our cohort had PDAC, IPMN, and MCN) because such a morphological finding in isolation does not justify a diagnosis of AIP, as duct-centered inflammation and increased IgG4+ plasma cells may be seen in a context that clinically is not AIP type 1, and this is even more relevant for cases of MCN or IPMN in which AIP type 2 was histologically diagnosed, as AIP type 2 has few morphological diagnostic criteria (no IgG4+ plasma cells, usually no storiform fibrosis, nor obstructing phlebitis), and at the same time, periductal inflammation with some neutrophils in the duct lumen is not uncommon as a nonspecific change [15].

Increasing the clinical dilemma (of whether to operate or not to operate), it is of note that AIP is a rare disease, and in contrast, PDAC is ranked as the 11th most common cancer in the world, representing 4.5% of all deaths caused by cancer in 2018 [17], with poor prognosis and 5-year overall survival across the whole patient population of only 9% [18]. In 2014, an international panel of pancreatic surgeons working in well-known, high-volume centers reviewed the literature and worked together to establish a consensus on when to perform a pancreatoduodenectomy in the absence of positive histology [6]. In the presence of a solid mass suspicious for malignancy,

consensus was reached that biopsy proof is not required before proceeding with resection. Confirmation of malignancy, however, is mandatory for patients with borderline resectable disease to be treated with neoadjuvant therapy before exploration for resection [6]. Furthermore, when a diagnosis of AIP is highly suspected, a biopsy was recommended, and a short course of steroid treatment should be considered if the biopsy does not reveal features suspicious for malignancy [6]. Despite the fact that response to GC is effective in AIP [15] and it has become part of the diagnostic criteria for AIP [1], a multidisciplinary team in our hospital made the decision of immediate surgical treatment in patients described in this study, as the possible mistake and delay in patients with PDAC will have disastrous consequences, and prompt surgical treatment is the only chance for survival. The decision of when to perform pancreatic surgery in patients with suspected malignancy on imaging and in the absence of positive histology is a big dilemma for clinicians all over the world [6]. The incidence of benign disease found on pathologic review after pancreatoduodenectomy for a presumed malignancy was reported as 5–13%, and by contrast, 5–9% of patients operated on for chronic pancreatitis showed malignancy in the final pathologic examination of the resected pancreas [6]. Based on the results of the review on pancreatoduodenectomy for presumed pancreatic cancer, surgeons should continue to rely on clinical judgment when reasonable efforts to obtain a preoperative tissue diagnosis have been unsuccessful because more than 80% of the time, a malignancy will be present [19]. A recently published systematic review identified 33 patients with PDAC and AIP, among them 33% synchronous and 67% metachronous [20].

Another important question arising from the data we presented relates to the rate of AIP relapse in operated patients. In all 7 patients with AIP type 2, surgery was definitive treatment as none of them had relapse of the disease in pancreatic remnants. In the group of patients with AIP type 1, complete remission after surgery was noted in 57% of the patients. In 9 (32%) patients with AIP type 1, relapses occurred in the pancreas and/or in other involved organs, and they were successfully treated with GC and/or rituximab. In a multicenter study of 114 surgically treated European AIP patients, the reported relapse rate for AIP type 1 was 41.2%, and for AIP type 2, it was 15.4% [21]. In a study from the USA, 74 patients with AIP were included in a retrospective analysis, and the reported recurrence rate was 17% [22]. On the other hand, a study from Japan of 13 patients after surgical treatment showed no relapse of AIP type 1 in the remnant pancreatic tissue after 5 years of follow-up [23]. Possible explanations for such a discrepancy between the different studies at least partially may be that results were impacted by the different sizes of the cohorts and heterogenous groups of the patients included in the study as well as the methodology. Relapse rate and postsurgical treatment in our study also included recurrence in other involved organs, as OOI was present in 71% of operated patients, mostly related to immune-related cholangitis, inflammatory bowel disease, kidneys, lungs, and vasculitis, which we have already reported in other publications of our research group [4, 5, 8, 9]. Unfortunately, in this subgroup of patients, OOI occurred after the initial diagnosis of AIP (after surgery), and we could not use it at the time of decision-making for surgery. However, later occurrence of OOI and treatment of relapses are of importance in confirmation of AIP diagnosis.

Retrospective analysis of medical records is an important limitation of the presented study, especially regarding the missing data on serum IgG4 levels before and after surgery. Prospective studies are necessary to elucidate the IgG4 serum-negative patients with AIP type 1 as well as the role of serum IgG4 values in monitoring of the disease course. This study's large sample size is its greatest strength.

Diagnosis of AIP is not always straight forward, and in some cases, it is not easy to differentiate AIP from malignant lesions. Surgery is generally not indicated for AIP; however, it must be considered in patients when suspicion of malignant/premalignant lesions cannot be excluded after complete diagnostic workup.

Acknowledgments

The present study is a part of Sara Nikolic's PhD project.

Statement of Ethics

The study was approved by the Clinic Ethical Committee in Stockholm (EPN Dnr. 2016/1571-31; Dnr. 2020-02209; Dnr. 2016/2542-31/1; Dnr. 2019-03345) and complies with the Declaration of Helsinki. Due to retrospective nature, the ethical committee approved the lack of informed consent form.

Conflict of Interest Statement

S.N.: Ferring (lecture fee), Mylan (lecture fee), and Krka (lecture fee); P.G.: none; R.P.M.: none; S.G.: none; F.B.S.: none; M.D.C.: industry grant (Haemonetics, Inc.) in study on pancreas

cancer, principal investigator of a sponsored Boston Scientific study on the use of intraoperative pancreatoscopy; E.S.: none; C.S.V.: FibroGen (consultancy); J.M.L.: Abbott (lecture fee) and Mylan (lecture fee); M.V.: Abbott (lecture fee) and Mylan (lecture fee).

Funding Sources

No funding was received for this study.

Author Contributions

Study conception and design: M.V. and J.M.L. Acquisition of data: S.N., M.V., and P.G. Interpretation of data and drafting of the manuscript: all. Guarantors of the article: M.V. and J.M.L. All authors approved the final version of the article, including the authorship list.

Data Availability Statement

All data retrieved and analyzed during this study are included in this article. Additional questions are to be addressed by the corresponding author upon inquiry.

References

1 Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011 Apr;40(3):352–8.
2 Klöppel G, Lüttges J, Löhr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: pathological, clinical, and immunological features. Pancreas. 2003 Jul;27(1):14–9.
3 Löhr JM, Beuers U, Vujasinovic M, Alvaro D, Frøkjær JB, Buttgereit F, et al. European guideline on IgG4-related digestive disease – UEG and SGF evidence-based recommendations. United European Gastroenterol J. 2020 Jul;8(6):637–66.
4 Vujasinovic M, Pozzi Mucelli RM, Valente R, Verbeke CS, Haas SL, Löhr JM. Kidney involvement in patients with type 1 autoimmune pancreatitis. J Clin Med. 2019 Feb 18; 8(2):258.
5 Nikolic S, Brehmer K, Panic N, Valente R, Löhr JM, Vujasinovic M. Cardiovascular and lung involvement in patients with autoimmune pancreatitis. J Clin Med. 2020 Feb 3; 9(2):409.
6 Asbun HJ, Conlon K, Fernandez-Cruz L, Friess H, Shrikhande SV, Adham M, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014 May;155(5):887–92.
7 Schneider A, Hirth M, Münch M, Weiss C, Löhr JM, Ebert MP, et al. Risk of cancer in patients with autoimmune pancreatitis: a single-center experience from Germany. Digestion. 2017;95(2):172–80.
8 Vujasinovic M, Valente R, Maier P, von Beckerath V, Haas SL, Arnelo U, et al. Diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden. Pancreatology. 2018 Dec;18(8):900–4.
9 Vujasinovic M, Maier P, Maetzel H, Valente R, Pozzi-Mucelli R, Moro CF, et al. Immunoglobulin G subtypes-1 and 2 differentiate immunoglobulin G4-associated sclerosing cholangitis from primary sclerosing cholangitis. United European Gastroenterol J. 2020 Jun; 8(5):584–93.
10 Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006 Sep;101(9):2070–5.
11 Oseini AM, Chaiteerakij R, Shire AM, Ghazale A, Kaiya J, Moser CD, et al. Utility of serum immunoglobulin G4 in distinguishing immunoglobulin G4-associated cholangitis from cholangiocarcinoma. Hepatology. 2011 Sep 2; 54(3):940–8.
12 Boonstra K, Culver EL, de Buy Wenniger LM, van Heerde MJ, van Erpecum KJ, Poen AC, et al. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. Hepatology. 2014 May; 59(5):1954–63.
13 Yoon SB, Moon SH, Kim JH, Song TJ, Kim MH. The use of immunohistochemistry for IgG4 in the diagnosis of autoimmune pancreatitis: a systematic review and meta-analysis. Pancreatology. 2020 Dec;20(8):1611–9.
14 Bateman AC, Culver EL. IgG4-related disease-experience of 100 consecutive cases from a specialist centre. Histopathology. 2017 Apr; 70(5):798–813.
15 Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J. 2017 Mar;5(2): 153–99.
16 Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012 Sep;25(9):1181–92.
17 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6): 394–424.
18 Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology. 2015 Jan–Feb;15(1):8–18.
19 Barone JE. Pancreaticoduodenectomy for presumed pancreatic cancer. Surg Oncol. 2008 Aug;17(2):139–44.
20 Macinga P, Bajer L, Del Chiaro M, Chari ST, Dite P, Frulloni L, et al. Pancreatic cancer in patients with autoimmune pancreatitis: a scoping review. Pancreatology. 2021 Aug; 21(5):928–37.
21 Detlefsen S, Zamboni G, Frulloni L, Feyerabend B, Braun F, Gerke O, et al. Clinical features and relapse rates after surgery in type 1 autoimmune pancreatitis differ from type 2: a study of 114 surgically treated European patients. Pancreatology. 2012 May–Jun;12(3): 276–83.
22 Clark CJ, Morales-Oyarvide V, Zaydfudim V, Stauffer J, Deshpande V, Smyrk TC, et al. Short-term and long-term outcomes for patients with autoimmune pancreatitis after pancreatectomy: a multi-institutional study. J Gastrointest Surg. 2013 May;17(5):899–906.
23 Miura F, Sano K, Amano H, Toyota N, Wada K, Kadowaki S, et al. Long-term surgical outcomes of patients with type 1 autoimmune pancreatitis. World J Surg. 2013 Jan;37(1): 162–8.