

# Differential EUS findings in focal type 1 autoimmune pancreatitis and pancreatic cancer: A proof-of-concept study

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## ABSTRACT

**Background and Objectives:** Autoimmune pancreatitis (AIP) often mimics pancreatic cancer (PC), particularly if presenting as a focal lesion. EUS may orient the differential diagnosis between them. This study aims to identify EUS findings that might be useful to differentiate type 1 focal autoimmune pancreatitis (f-AIP1) and PC. **Materials and Methods:** F-AIP1 and PC patients were retrospectively collected, matched, and compared. EUS findings considered were: focal mass echogenicity, loss of lobularity, distal atrophy, peripancreatic hypoechoic margins (PHM), pancreatic duct dilation, duct-penetrating sign (DPS), pancreatic/common bile duct thickened walls (PD/CBD-TW), and vessel infiltration (VI). Elastography findings were also recorded. Variables with a  $P < 0.05$  at univariate analysis were included in logistic multiple regression. **Results:** Fifteen patients with f-AIP and 60 with PC were studied. FE was hypoechoic in all patients from both groups. PHM was observed in 40% of f-AIP1 cases but not in PC ones ( $P < 0.001$ ). DPS was found in 10/15 (66.7%) f-AIP1 and in 7/60 (11.7%) PC patients ( $P < 0.001$ ). PD-TW and CBD-TW were observed in 66.7%/60% f-AIP1 cases and in 6.7%/13.6% PC patients, respectively ( $P < 0.001$  for both comparisons). Pancreatic masses were significantly different at EUS elastography (elastic respectively in 71.4% f-AIP1 and 3.8% PC,  $P < 0.001$ ). VI was suspected in 20% of f-AIPs and 85% of PCs ( $P < 0.001$ ). At multiple regression, PD-TW, CBD-TW, elastic pattern, and the absence of VI independently supported a diagnosis of f-AIP1. **Conclusions:** Our results suggest that EUS findings deserve consideration in the diagnostic workup of AIP to improve the differential diagnosis with PC.

**Key words:** autoimmune pancreatitis, contrast, diagnosis, elastography, EUS, PDAC

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## BACKGROUND

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis with specific diagnostic criteria and treatment approaches. AIP can occur exclusively as a primitive pancreatic disorder or in association with other systemic diseases with presumed autoimmune etiology, such as retroperitoneal fibrosis, salivary gland disorder, cholangitis, tubulointerstitial disease, and inflammatory bowel disease (IBD).<sup>[1-4]</sup> According to the International Consensus Diagnostic Criteria (ICDC),<sup>[5]</sup> AIP is classified as either type 1 or type 2, with the former, also named lymphoplasmacytic sclerosing pancreatitis, representing the pancreatic manifestation of immunoglobulin G (IgG4)-related systemic disease.<sup>[6]</sup> Type 1 AIP preferentially occurs in elderly men, often associates with extrapancreatic manifestations and increased serum IgG4 concentration, and typically shows a prominent pancreatic infiltration of IgG4-positive plasma cells.<sup>[7,8]</sup> Type 2 AIP, also known as idiopathic duct-centric pancreatitis, is, instead, more evenly distributed between the sexes, occurs at a lower age, frequently associates with IBDs, and shows distinct granulocytic epithelial lesions on histological examination.<sup>[9]</sup>

AIP can present with either a diffuse or a focal form and mimics pancreatic cancer (PC) in the majority of its clinical, especially when presenting as a focal tumor-like mass.<sup>[10-12]</sup> Magnetic resonance imaging (MRI), computed tomography scan (CT-scan), and EUS can all provide useful information for supporting a diagnosis of AIP. Yet, according to available guidelines, only specific MRI and CT-scan findings are considered central to the diagnostic workup while EUS, despite providing equally informative morphologic features, is mainly performed for obtaining cytohistologic specimens.<sup>[5,13,14]</sup> To our knowledge, few studies have comprehensively evaluated EUS findings of AIP, but none has assessed the sensitivity and specificity of these morphologic features in the differential diagnosis with PC.<sup>[15-18]</sup>

In the present observational monocentric study, we aimed to identify pancreatic and peripancreatic EUS findings typical of type 1 focal AIP (f-AIP1) and to assess their utility in the differential diagnosis with PC.

## MATERIALS AND METHODS

### *Study design and patients*

This is a monocentric, retrospective case-control study including patients with a “definitive” diagnosis

of f-AIP1 according to the ICDC guidelines who underwent EUS in San Raffaele Hospital (Milan) between May 2008 and February 2020.<sup>[5]</sup> Data were retrospectively collected according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.<sup>[19]</sup> Inclusion criteria for AIP patients were definitive f-AIP1; age >18 years; and images and videos of EUS procedure available. A cohort of contemporary patients from San Raffaele Hospital histologically diagnosed with localized PC was used as comparator. We excluded patients with advanced stage disease or metastatic one. To avoid possible selection biases, patients and controls were matched for age, sex, location of the focal mass, and year of EUS examination. All patients provided written informed consent and data were recorded in compliance with the pan-immuno protocol specifically approved by the San Raffaele Hospital Ethics Committee (registry number: 22/INT/2018).

### *EUS*

EUS examinations were performed by expert endosonographers with a linear array echoendoscope (Pentax EG-3870UTK; Pentax Europe, Hamburg, Germany) under deep sedation with anesthesiologist assistance. All images and videos of the procedures were revised by two independent endosonographers (MT and PZ). Disagreement was solved by discussion with a third expert endoscopist (MCP). Contrast-enhanced EUS (CE-EUS) was performed by injecting in a peripheral vein 5 ml of microbubble contrast agent SonoVue (Bracco Imaging, Milan, Italy) followed by 10 ml of saline. A video of the contrast sequence was recorded for 2 min after the injection and images were all re-evaluated by the two operators. The enhancement intensity was defined as hyper to iso-or hypo-enhancement. Hyper- to iso-enhancement was defined when enhancement intensity was superior or similar to the adjacent parenchyma. EUS elastography was performed using the software embedded in the ultrasound system. A region of interest containing at least 50% of the target lesion was identified and elastography images were recorded. Two authors revised all the images and classified the target lesion as rigid or elastic.

The following EUS features were evaluated: (1) parenchymal features including focal mass echogenicity, loss of lobularity, distal atrophy (DA), and peripancreatic hypoechoic margins (PHM); (2) pancreatic duct (PD) features including PD dilation, thickening

of PD walls, and duct-penetrating sign (DPS), defined as visible unobstructed PD that penetrates into the mass; (3) common bile duct (CBD) features including thickening of CBD walls; and (4) peripancreatic features, such as vessel infiltration (VI). In addition, CE-EUS and elastography features were recorded.

### Statistical analysis

Simple size calculation was performed ahead considering the subsequent radiological and EUS features that may differentiate f-AIP1 from PC according to available literature:<sup>[15,16,20,21]</sup> CBD thickened walls (TW), PHM, and duct-penetrating sign. Considering an estimated odds ratio of 0.06, 0.02, and 0.015 (expected percentage differences: 45%, 40%, 45%) and an alpha-error of 0.05 and a beta-error of 0.20, at least 15 cases and 60 controls were needed.

Data for continuous variables were presented as mean and standard deviation for variables with normal distribution or as median and interquartile range (IQR) for variables with skewed distribution; data for categorical variables were presented as frequency and percentage. Differences between continuous data were analyzed by Mann–Whitney U-test and Chi-square test was used for dichotomous or categorical variables. The univariate and multivariate logistic regression models were used to assess the independent predictive factors of AIP and PC diagnosis. Variables with a  $P < 0.1$  at univariate analysis were included in the multivariate model. A correct diagnosis of AIP was considered as the outcome variable and all the EUS features were

investigated as potential explanatory variables.  $P < 0.05$  was considered statistically significant. Statistical analysis was conducted using MedCalc Statistical Software Version 12.5.0 (MedCalc Software LTD, Ostend, Belgium).

## RESULTS

### Patients' characteristics

We retrospectively identified 15 cases with a definitive diagnosis of f-AIP1 meeting inclusion criteria and 60 matched PC patients. Baseline features of f-AIP1 and PC cases are reported in Table 1. The median age at diagnosis in patients with f-AIP1 was 69 years (IQR 62.5–75) and only two patients were females (13.4%). The focal mass was located in the head of the pancreas in 80% of cases and, accordingly, the most common onset symptom was jaundice. In 6 of 10 jaundiced patients, a biliary stent was placed before performing EUS at our center. The distribution of age, sex, location of the mass, previous biliary stent placement, and onset of symptoms was similar between patients with f-AIP1 and PC.

### EUS findings

#### Parenchymal findings in autoimmune pancreatitis and pancreatic cancer

DA was present in 26.6% of f-AIP1 and in 38.3% of PC ( $P = 0.59$ ). PHM were observed in 40% of f-AIP1 but not in PC ( $P < 0.001$ ). EUS elastography was performed in 14/15 f-AIP1 patients and in 53/60 PC patients. According to strain histogram

**Table 1. Baseline features of focal autoimmune pancreatitis type 1 and pancreatic cancer patients included in the study**

	f-AIP type 1 patients (n=15), n (%)	PC patients (n=60), n (%)	Univariate analysis (P)
Age (years), median (range)	68.8 (62.8-74.8)	66.9 (64.1-69.6)	0.53
Sex			
Male	13 (86.6)	46 (76.6)	0.62
Asymptomatic	4 (26.6)	10 (16.7)	0.60
Onset symptoms			
Jaundice	10 (66.7)	32 (53.3)	0.52
Abdominal pain	3 (20.0)	15 (25.0)	0.94
New onset diabetes	2 (13.3)	6 (10.0)	0.70
Weight loss	0	5 (8.3)	0.56
Biliary stent placement before EUS examination	6 (40.0)	17 (28.3)	0.57
Location focal mass			
Head/uncinate process	12 (80.0)	48 (80.0)	0.99
Body/neck	2 (13.3)	8 (13.3)	0.86
Tail	1 (6.7)	4 (6.7)	0.99
Hypochoic mass	15 (100)	60 (100)	0.99

f-AIP: Focal autoimmune pancreatitis; PC: Pancreatic cancer

and/or strain ratio, focal masses were considered elastic in 10/14 (71.4%) f-AIP1 patients and rigid in 51/53 (96.2%) PC cases ( $P < 0.001$ ). CE-EUS was available in 13/15 (86.7%) f-AIP1 and in 33/60 (55.0%) PC patients. In these patients, the focal mass was hypoenhancing in 15.4% f-AIP1 and 90.9% of PC cases ( $P < 0.001$ ).

### Ductal and extrapancreatic findings in autoimmune pancreatitis and pancreatic cancer

Pancreatic duct dilation (PDD) was observed in 6/15 f-AIP1 (40.0%) and in 46/60 PC patients (76.7%;  $P = 0.01$ ). The maximal median PDD diameter was 5.0 mm (IQR 5.0–5.75) in f-AIP1 and 5.5 mm (IQR 5.75–8.0) in the PC group ( $P = 0.65$ ). The DPS was present in 10/15 f-AIP1 and in 7/60 PC patients ( $P < 0.001$ ). The thickened PD walls were observed in 6.7% of patients with PC and in 66.7% of f-AIP1 ones ( $P < 0.001$ ). The rate of CBD-TW was significantly higher in f-AIP1 compared to PC (60.0% vs. 13.6%;  $P < 0.001$ ). VI was found in 20% of f-AIP1 patients and in 85% of PC cases ( $P < 0.001$ ).

### Variables associated with the f-AIP1 diagnosis at logistic regression analysis

Only variables with  $P < 0.1$  at univariate analysis were included in the logistic regression analysis. A correct diagnosis of AIP was considered as the outcome variable, and all the EUS features were investigated as potential explanatory variables. At univariate and multivariate analysis, thickened PD and CBD walls, elastic pattern of the pancreatic mass at EUS elastography, and absence of vessels infiltration were associated with the diagnosis of f-AIP1 [Table 2]. Table 3 reports the diagnostic accuracy of these four independent predictive variables for the diagnosis of f-AIP1. When at least two of these features were present, sensitivity, specificity, positive predictive values, and negative predictive values were respectively 86.7%, 96.7%, 86.7%, and 96.7%. Figures 1 and 2 show peculiar EUS findings in f-AIP1 and PC patients.

## DISCUSSION

f-AIP1 is a rare disease with multifaceted clinical and radiological presentation. Differential diagnosis of AIP

**Table 2. Univariate and multivariate analysis of features predictors of focal autoimmune pancreatitis type 1 diagnosis**

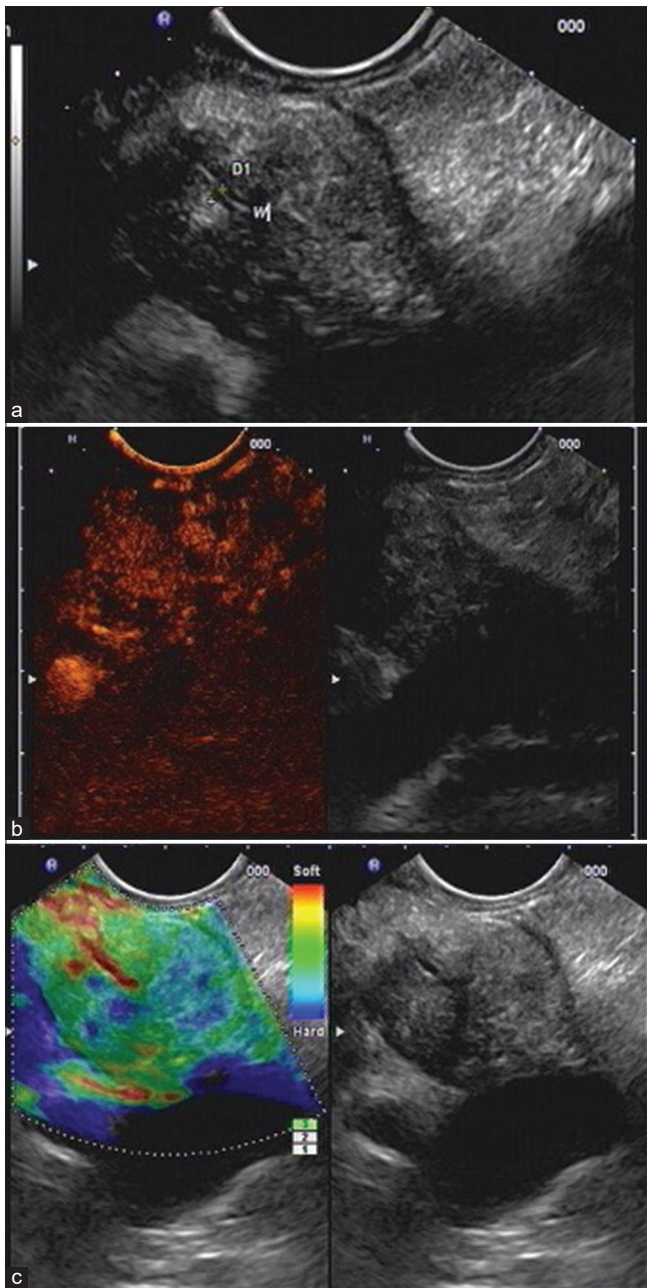
	f-AIP type 1 patients (n=15), n (%)	PC patients (n=60), n (%)	Univariate analysis (P)	Multiple regression (P)
LL	10 (66.7)	60 (100)	0.99	
DA	4 (26.6)	23 (38.3)	0.59	
PHM	6 (40.0)	0	<0.001	
PDD	6 (40.0)	46 (76.7)	0.01	
DPS	10 (66.7)	7 (11.7)	<0.001	
Thickened PD walls	10 (66.7)	4 (6.7)	<0.001	0.01
Thickened CBD walls	9 (60.0)	8 (13.6)	<0.001	0.002
Lymphadenopathies	14 (93.3)	44 (73.3)	0.19	
VI	3 (20.0)	51 (85.0)	<0.001	<0.001
Hypoenhancement	2 (on 13: 15.4)	30 (on 33: 90.9)	<0.001	
Soft pattern at EUS elastography	10 (71.4)	2 (3.8)	<0.001	0.004

f-AIP: Focal autoimmune pancreatitis; PC: Pancreatic cancer; LL: Loss of lobularity; DA: Distal atrophy; PHM: Peripancreatic hypoechoic margins; DPS: Duct-penetrating sign; PD: Pancreatic duct; PDD: PD dilation; CBD: Common bile duct; VI: Vessel infiltration

**Table 3. Sensitivity analysis for predictors of focal autoimmune pancreatitis type 1 diagnosis resulted significant at multiple regression**

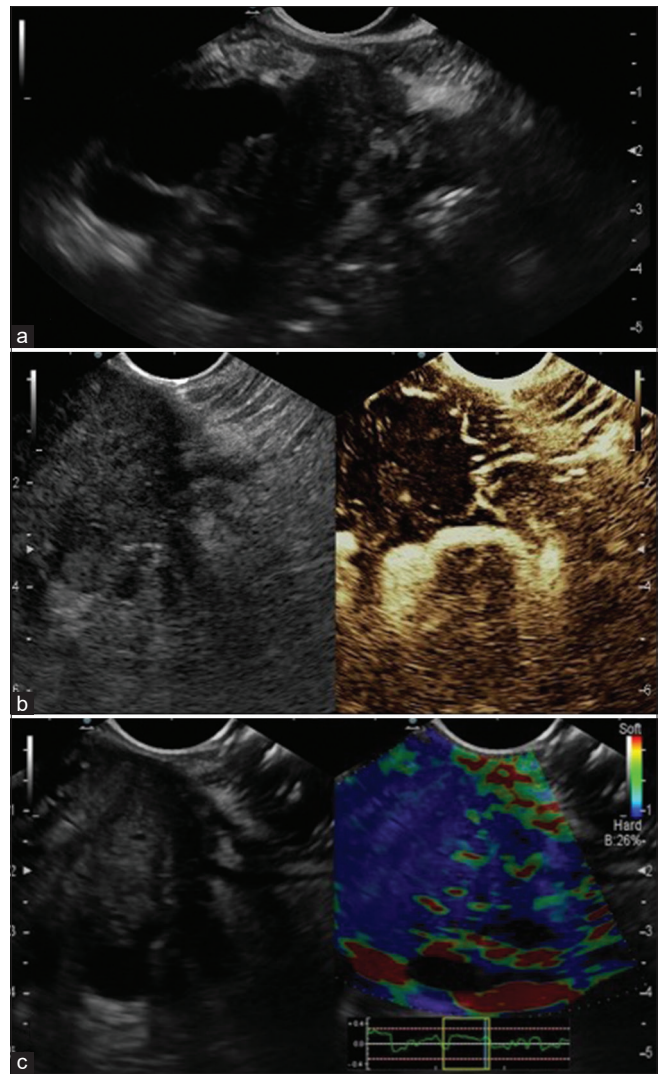
	PD thickening walls	CBD thickening walls	Absence of vessels infiltration	Soft pattern at EUS elastography	Presence of at least 2 of 4 predictive factors
Sensitivity	66.7 (38.4-88.2)	60.0 (32.3-83.7)	80.0 (51.9-95.7)	71.4 (41.9-91.6)	86.7 (59.5-98.3)
Specificity	93.3 (83.8-98.1)	86.4 (75.0-94.0)	85.0 (73.4-92.9)	96.2 (87.0-99.5)	96.7 (88.5-99.6)
Positive likelihood ratio	10.0 (3.63-27.5)	4.43 (2.06-9.51)	5.33 (2.77-10.2)	18.9 (4.67-76.7)	26.0 (6.56-103.0)
Negative likelihood ratio	0.36 (0.17-0.73)	0.46 (0.25-0.87)	0.24 (0.09-0.65)	0.30 (0.13-0.68)	0.14 (0.04-0.50)
Positive predictive value	71.4 (47.6-87.3)	52.9 (34.3-70.7)	57.1 (41.0-71.9)	83.3 (55.2-95.3)	86.7 (62.1-96.3)
Negative predictive value	91.8 (84.5-95.8)	89.5 (81.9-94.1)	94.4 (86.0-97.9)	92.7 (84.8-96.7)	96.7 (88.9-99.1)

PD: Pancreatic duct; CBD: Common bile duct



**Figure 1.** Typical endosonographic findings in patients with focal autoimmune pancreatitis type 1: (a) Duct-penetrating sign, (b) hyperenhancing focal lesion and (c) soft EUS elastographic pattern

can thus be very challenging both in its diffuse and focal presentation. The international consensus criteria for the diagnosis of AIP<sup>[5]</sup> highlight the relevance of some radiological (CT or MRI) features for diagnostic purposes, such as diffuse or focal enlargement of the pancreas with delayed enhancement or segmental/long stricture or PD narrowing with no upstream dilation. In this consensus document, however, the possible role of “crude” EUS imaging findings is not considered. Similarly, in the recently published UEG guidelines on pancreatobiliary IgG4-related disease,<sup>[14]</sup> EUS is



**Figure 2.** Typical endosonographic findings in patients with pancreatic cancer: (a) Pancreatic duct dilation, (b) hypoenhancing focal lesion, and (c) rigid EUS elastographic pattern

only mentioned as a method to obtain a pathological diagnosis and to exclude PC.

However, the accuracy of EUS-FNA (EUS-fine-needle aspiration) to obtain a diagnosis of AIP is still limited. A recent meta-analysis showed that cytology obtained by EUS-FNA needles is diagnostic in only 54.7% of cases, and the diagnostic yield of histological examination through FNA is of 21.9%.<sup>[22]</sup> For this reason, we retrospectively revised reports, images, and videos of patients with f-AIP1 who underwent EUS in our center to identify possible EUS features that could support the differential diagnosis of AIP from PC.

In our study, the absence of VI, an elastic pattern of the pancreatic mass at EUS elastography, and the presence of TW of both the pancreatic and common biliary

ducts were associated with f-AIP1 diagnosis compared to PC. By definition, PC is able to invade surrounding or distant structures and vascular infiltration is present in about 90% of cases. EUS has good sensitivity and specificity in diagnosing vascular invasion (85% and 91%, respectively).<sup>[23]</sup> The present finding of VI in 20% of AIP cases, however, is not surprising, as the presence of the IgG4-related retroperitoneal fibrosis can mimic vascular invasion. Similar findings were reported by Farrell *et al.*<sup>[16]</sup> with a 23% rate of vascular involvement in a cohort of 14 AIP patients, not distinguished by type.

In the present study, an elastic pattern on EUS elastography was reported in 71.4% of f-AIP1 patients and only 3.8% of PC ones and turned out to be a significant factor associated with AIP diagnosis. While elastography is increasingly employed as a tool to increase the diagnostic accuracy of EUS in different settings, its use for the diagnosis of AIP is still limited.<sup>[24]</sup> A meta-analysis by Mei *et al.*<sup>[25]</sup> evaluated the accuracy of EUS elastography for the diagnosis of solid pancreatic masses and the pooled sensitivity, specificity, and diagnostic odd ratio were respectively 0.95, 0.67, and 42.3 for distinguishing benign from malignant solid masses. Dietrich *et al.*<sup>[26]</sup> reported a characteristic stiff elastographic pattern in 5 AIP cases not only in the correspondence of the focal mass, but also in the surrounding parenchyma. These findings were also confirmed by a preliminary study that analyzed the stiffness of the pancreatic mass using MRI.<sup>[27]</sup>

The evaluation of the PD and CBD diameter and wall thickness is considered among the main radiological diagnostic features of AIP.<sup>[28,29]</sup> In the present study, at the multivariate regression analysis, we found a significant association between the thickness of both PD and CBD and f-AIP1 diagnosis. As IgG4-related disease is a systemic inflammatory disease with possible involvement of the CBD, walls thickening could pose the suspicion of AIP diagnosis, especially in patients without clinical cholangitis. Indeed, IgG4-positive plasma cells can infiltrate the CBD wall, while a CBD dilation can occur in cases of stenosis due to a mass, both in case of PC or AIP. As far as regards pancreatic duct features, the dilatation is a cardinal sign of PC that, although less commonly, may also occur in f-AIP1, while the DPS is less frequent in PC and more frequently associated with AIP. In the present study, the DPS was present in 66.7% of f-AIP1 patients and in only 11.7% of PC ones.<sup>[15]</sup>

There have been few previous studies investigating EUS features of AIP. Hoki *et al.*<sup>[15]</sup> compared EUS

features of 25 AIP (both type 1 and type 2) and 30 PC patients, with the presence of focal hypoechoic area, extrahepatic bile duct wall thickening, PHM, and the DPS all more common in AIP, in keeping with our findings. However, in that study, both focal and diffuse AIP were included and elastography or contrast-enhancement were not evaluated. Several studies investigated the vascular behavior of AIP after EUS with CE-EUS. Imazu *et al.*<sup>[30]</sup> reported that focal AIP had a peak intensity and a maximum intensity gain significantly higher compared to PC masses. Finally, Cho Min Keun *et al.*<sup>[31]</sup> also aimed to define vascular features of AIP with respect to PC, showing that f-AIP are hyper-/iso-enhancing in the arterial phase compared to PC (89% *vs.* 13%), with more commonly a homogeneous contrast agent distribution (81% *vs.* 17%), and absent irregular internal vessels (85% *vs.* 30%).

In the present study, almost the totality of PC patients had a hypoechoic lesion compared to the iso- or hyperechoic f-AIP1 masses. Despite these promising results at the univariate analysis, CE-EUS findings were not included in the multiple regression model, likely due to the lack of data in a part of PC patients. The limited use of CE-EUS in our center is related with the availability of Rapid On-Site Evaluation, during EUS-FNA with dedicated pathologists and cyto-technicians, which makes the use of CE-EUS usually useless in most PC cases.

The present study has some strengths, such as the homogeneous enrollment of cases of f-AIP1 that pose a tricky differential diagnosis with PC, especially when the cytohistological examination is not conclusive. For this reason, two matched groups of patients with a certain diagnosis were chosen. We hypothesized that some features could have a different prevalence in cases and controls and accordingly performed a power calculation, which also partially reflects the actual much lower prevalence of f-AIP1 compared to PC. In addition, this is one of the few studies investigating elastography patterns of AIP as reported by expert ultrasonographers and it is, to date, the only one that considers only patients with focal type 1 AIP.

Our study also carries some limitations, including the retrospective design and the small sample size, especially for f-AIP1 patients. It is therefore possible, considering the differences observed in the univariate analysis, that the study is underpowered to obtain significant differences for variables other than TW of PD and CBD, elastographic

pattern and vascular infiltration. The recruitment of only patients with a certain diagnosis of f-AIP1 is also a possible bias, as patients in whom radiology and EUS gave falsely positive or negative diagnoses were excluded. Our choice was driven by the pragmatic aim to identify morphologic features associated with f-AIP1 compared to PC. The present findings, however, need validation in a prospective setting with an appropriate number of unselected patients. Finally, as for any study performed in a tertiary center, these findings need to be considered with caution as they may not be replicated in different clinical settings.

## CONCLUSIONS

Our study suggests that EUS represents a useful method to distinguish f-AIP1 from PC, not only for the capacity to obtain cyto/histological samples but also for the possibility to identify during the same endoscopic procedure at no additional discomfort to the patient morphological features that may specifically support a diagnosis of AIP on top of established MRI and CT findings. Given the relevant clinical and therapeutic implications of misdiagnosing PC in a patient with f-AIP1, further prospective studies are needed to validate these preliminary findings and to support the inclusion of EUS findings among variables considered for the diagnosis of AIP.

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Nil.

## Conflicts of interest

Arcidiacono Paolo Giorgio is an Associate Editor of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and his research groups.

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