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Advances in endoscopic ultrasound for autoimmune pancreatitis: Tissue acquisition, imaging innovations, artificial intelligence, and multidisciplinary integrations

Braimakis I *et al.* EUS in AIP

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Abstract

Autoimmune pancreatitis (AIP) is an immune-mediated inflammatory condition of the pancreas that can be difficult to differentiate from pancreatic malignancy and therefore remains challenging to diagnose. Type 1 AIP is the pancreatic manifestation of immunoglobulin G subclass 4-related disease and can be associated with other systemic fibro-inflammatory conditions. Type 2 AIP is characterised histologically by granulocytic epithelial lesions and is frequently associated with inflammatory bowel disease. Over the previous years, endoscopic ultrasound (EUS) has become an important part of the diagnostic work-up of patients presenting with suspected AIP, particularly when imaging studies demonstrate focal pancreatic enlargement, or a mass-like lesion. Recent advances in EUS imaging, including contrast-enhanced harmonic EUS and EUS elastography, may improve characterisation of the pancreatic lesion and help distinguish an inflammatory pancreatic process from a pancreatic malignancy. Moreover, EUS-guided tissue acquisition plays an important role in this context by allowing histological assessment of the lesion and hence helping exclude a malignancy. EUS-guided fine-needle biopsy is currently the preferred tissue acquisition technique, as it allows the preservation of tissue architecture, which helps facilitate the diagnosis of AIP. A multidisciplinary approach involving a panel of specialists in hepatopancreatobiliary endoscopy, hepatology, rheumatology, radiology, cardiology, nephrology, and histopathology is valuable for integrating the different components of the diagnostic work-up and guiding subsequent management. Finally, emerging artificial intelligence algorithms for EUS may support the diagnostic process and facilitate recognition of AIP. This review discusses current and emerging EUS techniques, tissue acquisition options, safety considerations, multidisciplinary integration and the potential role of artificial intelligence in the diagnosis and management of AIP.

Key Words: Autoimmune pancreatitis type 1; Autoimmune pancreatitis type 2; Endoscopic ultrasound; Immunoglobulin G subclass 4-related disease; Artificial intelligence

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Core Tip: Endoscopic ultrasound (EUS) is central to the diagnostic work-up of autoimmune pancreatitis, particularly in patients with focal pancreatic enlargement or mass-like lesions. Advances in EUS imaging and EUS-guided fine-needle biopsy using end-cutting needles may improve lesion characterisation and diagnostic accuracy by preserving tissue architecture. Artificial intelligence has the potential to further enhance EUS interpretation and reduce interobserver variability. Given the diagnostic complexity and need to exclude malignancy, multidisciplinary collaboration is valuable for integrating imaging, histology, serology and clinical findings and for guiding subsequent correct diagnosis and management.

INTRODUCTION

During the past few decades our understanding of the entity called autoimmune pancreatitis (AIP) has increased dramatically. Since 1995, when Yoshida *et al*[1] proposed the concept of AIP, a significant number of studies provided insight into this pancreatic disorder. We now know that AIP is a chronic inflammatory condition of the pancreas that is considered a discrete type of pancreatitis[2]. The International Consensus Diagnostic

Criteria (ICDC) defined AIP further as an immune-mediated benign pancreatic disease that manifests clinically with obstructive jaundice with or without a pancreatic mass, is characterised histologically by lymphoplasmacytic infiltrate and fibrosis and therapeutically by a response to steroids[3]. AIP is subclassified into 2 distinct types, AIP type 1 and type 2, where each demonstrates a different clinical and histopathological profile.

AIP type 1 is considered part of the systemic autoimmune fibro-inflammatory disease called immunoglobulin G subclass 4-related disease (IgG4-RD) and constitutes its pancreatic manifestation[4]. Its main histological features consist of periductal lymphoplasmacytic infiltration, storiform fibrosis, profuse immunoglobulin G subclass 4 [IgG4 (+)] plasma cells and obliterative phlebitis[3,5]. It is correlated with increased serum IgG4 levels[3]. IgG4-RD can involve a number of different organs, including pancreas (AIP type 1), bile ducts (IgG4-related cholangitis), retroperitoneum (IgG4 related fibrosis), salivary glands (IgG4 related sialadenitis), IgG4 related parotitis, kidneys (IgG4 related kidney disease, tubulointerstitial nephritis), IgG4 related lymphadenopathy, thyroid (IgG4 related thyroiditis), lungs (IgG4 related lung disease) and more[6-8]. Given its recent recognition, its prevalence is still not well defined. However, a male predominance has been demonstrated[9]. AIP type 1 is more frequently diagnosed than AIP type 2, accounting for approximately 92% of cases in a large international multicentre study, although AIP type 2 was more frequently reported in European and North American centres than in Asian centres[10].

On the contrary, AIP type 2, is a solely pancreas-related disease. The demonstrated histopathology pattern in AIP type 2 is idiopathic duct-centric pancreatitis[3]. It is characterised by the presence of granulocytic epithelial lesions in pancreatic acini, as well as in small/medium pancreatic ducts[11]. A correlation with inflammatory bowel disease has been exhibited in about 15%-30% of AIP type 2 cases[4]. When compared to AIP type

1, it usually affects younger patients, while no gender predominance has been demonstrated[5].

LITERATURE SEARCH

This is a narrative, non-systematic review. The review of the relevant literature was performed through a search of PubMed/MEDLINE. The terms “autoimmune pancreatitis”, “IgG4-related disease”, “endoscopic ultrasound”, “EUS-elastography”, “contrast-enhanced harmonic EUS”, “fine-needle biopsy”, “tissue acquisition” and “artificial intelligence”, were used to identify the literature discussed in this review, covering the literature up to March 2026. Priority was given in including systematic reviews, meta-analyses as well as landmark primary studies and society-guidelines. Conference abstracts and non-English-language publications were not included in this review. The article selection was based on the authors’ clinical judgement rather than a pre-specified protocol and this non-systematic approach is considered an inherent limitation of the narrative review format. Where AIP-specific data were lacking, evidence from studies of solid pancreatic masses in general is cited and reported as such.

DIAGNOSTIC CRITERIA OF AIP

Since the establishment of AIP and its subtypes as distinct disease entities, the primary objective has been to develop diagnostic algorithms that would guide the diagnostic work-up and help reduce the under-recognition of the disease. This goal was achieved with the introduction of the ICDC in 2011[3]. The ICDC established two different levels (level 1 and level 2) for the diagnostic criteria of AIP type 1, which include pancreatic parenchymal imaging, ductal imaging, serological tests with increased IgG4 serum levels, other organ involvement (OOI), histological findings, and response to steroid treatment[3]. Regarding AIP type 2, the ICDC also introduced two levels of diagnostic

criteria, which in this case again include parenchymal imaging, ductal imaging, OOI, histology, and response to treatment, but not serological tests[3].

HISTOPATHOLOGICAL AND IMAGING FEATURES OF AIP

Histopathological features

Of note, while AIP type 1 can, in some cases, be diagnosed without the need for biopsy acquisition, this is not the case for the diagnosis of AIP type 2 that entails histology of the pancreas[7]. Nevertheless, biopsy can be necessary in both subtypes to safely differentiate AIP from suspected pancreatic cancer or other malignancies[12].

There are four principal histopathological characteristics in AIP type 1[13]. Diffuse or patchy lymphoplasmacytic infiltration of the lobules and ducts is identified, with or without the presence of eosinophils[14,15]. Storiform fibrosis established around ducts and veins and obliterative phlebitis of pancreatic veins are other distinctive features of AIP type 1[15,16]. Finally, dedicated immunohistochemical staining for IgG/IgG4 should be performed, especially in cases presenting with tumour-like lesions with lymphoplasmacytic infiltration[17]. The presence of more than 10 IgG4+ plasma cells per high-power field in biopsy specimens and more than 50 IgG4+ plasma cells/high-power field in surgical tissue sample, are considered indicative of AIP type 1[15]. Estimating the IgG4/total IgG ratio, could further support an AIP type 1 diagnosis, with the cut off being a ratio of more than 40%[4,15].

The main histological features of AIP type 2 are the presence of sparse or the complete absence of IgG4+ plasma cells in biopsies on immunostaining and the existence of granulocytic epithelial lesions in pancreatic ducts[15,16]. AIP type 2 biopsies can in rare occasions demonstrate storiform fibrosis and obliterative phlebitis, but these are much less common when compared to AIP type 1 cases[3,4].

Morphological features of AIP - cross sectional imaging

As stated in the ICDC as well as in most published studies on this topic, the pancreas morphologic features are highly significant in reaching the diagnosis of AIP[3]. The typical features on imaging studies, include a diffusely enlarged pancreatic gland with loss of lobulation, usually referred to as 'sausage-like pancreas'[15]. This enlargement can in some instances also be associated with a capsule-like, thin, peripancreatic rim, often referred to as halo sign[5]. However, enlargement could also be focal or segmental, which is more common in AIP type 2, while diffuse enlargement is mainly encountered in AIP type 1[15]. Other imaging features suggestive of an AIP diagnosis, include a long, greater than 1/3, or multifocal main pancreatic duct stricture, that is however not associated with upstream dilatation of the duct[15,18,19]. In terms of differentiating AIP type 1 from type 2, this is not easily attainable with imaging studies, since both types share similar features[18]. Nevertheless, features that may facilitate the differentiation include more frequent presence of diffuse glandular enlargement in AIP type 1[20], the presence of cut-tail sign more suggestive of AIP type 2[21,18] and the detection of involvement of other organs on magnetic resonance imaging, indicative of AIP type 1[22].

Sonographical features of AIP - the role of endoscopic ultrasound

In addition to cross-sectional imaging studies, endoscopic ultrasound (EUS) is another diagnostic modality that provides additional evidence to substantiate the diagnosis of AIP and differentiate from pancreatic cancer, especially in cases presenting with focal pancreatic swelling. This is achieved both through the acquisition of biopsy samples and with the identification of pancreatic structural features that are suggestive of AIP[15].

Even though the sonographical features of EUS that are indicative of AIP are not part of the diagnostic criteria for AIP[3], these have been evaluated in several studies. Features comprising the diffuse hypoechoic glandular swelling in diffuse AIP, or a focal hypoechoic area in AIP cases with focal enlargement are considered typical sonographical features in AIP[4,23]. The typical EUS features of chronic pancreatitis,

based on Rosemont criteria[24], including hyperechoic foci and lobulations, are rarely noted[23-26]. Other sonographic features, including diffuse pancreatic enlargement, focal enlargement, bile duct thickened wall (TW), peripancreatic hypoechoic margins (capsule like rim) and lymphadenopathy, have also been evaluated in the context of association with AIP, with diffuse pancreatic enlargement, bile duct TW and peripancreatic hypoechoic margins being identified more frequently in AIP compared to pancreatic cancer cases[25]. Another study by Guo *et al*[27] specifically compared the sonographic features of focal AIP and pancreatic cancer and reported that diffuse hypoechoic pancreas, peripancreatic hypoechoic rim, bile duct TW along with hyperechoic stranding and lobulation were more suggestive of focal AIP, while vascular invasion, main pancreatic duct dilatation and focal hypoechoic mass were more in keeping with pancreatic cancer. Tacelli *et al*[28] not only found that presence of TW of bile ducts and the absence of vascular invasion were indicative of AIP and in specific AIP type 1, but reported as a supportive feature, namely the presence of pancreatic duct TW.

EUS elastography

Another EUS technique, the EUS elastography has been used to characterise pancreatic tissue, by determining its stiffness. It is widely recognized that different pancreatic lesions present different tissue hardness on EUS elastography[29-31]. In a study by Giovannini *et al*[29], EUS elastography was reported to demonstrate a sensitivity of 100% and a specificity of 67% for the diagnosis of pancreatic malignancies, according to the demonstrated elastographic pattern. In the same study, EUS elastography was also found to identify malignant lymph nodes, with sensitivity and specificity being 100% and 50% respectively. A study by Iglesias-Garcia *et al*[30] also advocated the value of EUS elastography in differentiating malignant lesions from benign ones, based on the elastographic pattern. In particular, a homogenous or heterogenous “green” pattern was found to rule out malignant lesion, while a homogenous or heterogenous “blue” pattern

was more in keeping with malignant mass. Specifically, regarding focal AIP type 1, a soft elastographic pattern was reported in 10 of 14 patients in a small series and was viewed as suggestive of AIP, while increased stiffness is reported more common in pancreatic adenocarcinoma[28]. On the contrary, in a small series by Dietrich *et al*[32], all five AIP cases were characterized by a stiff elastographic pattern, that was not only evident in the focal lesion but also in the whole pancreatic parenchyma. This interesting characteristic was not pertinent to the well demarcated adenocarcinoma cases, assisting the differential diagnosis between the 2 entities. It is, however, worth noting that as demonstrated in a prospective single-centre study by Dawwas *et al*[33], the diagnostic value of EUS elastography in differentiating pancreatic masses was limited. Therefore, it is more likely to serve as a complementary tool rather than a replacement for tissue acquisition.

These observed, apparently discrepant findings across studies, as the dissimilar elastography patterns reported by Tacelli *et al*[28] and Dietrich *et al*[32] for AIP, may reflect differences in pattern selection, elastography equipment and scoring systems, and the small, largely single-centre design of most available series, although genuine biological differences cannot be excluded. Therefore, a soft or a stiff elastographic pattern, can neither confirm nor exclude AIP. Given this heterogeneity, EUS- elastography findings should best be interpreted with caution and regarded as supportive rather than diagnostic.

Contrast (enhanced) harmonic EUS

Another EUS technique used to characterize pancreatic lesions is the contrast (enhanced) harmonic EUS (CH-EUS). The administration of a contrast agent improves the ability of EUS to identify a mass and its margins, to distinguish a vascular from a non-vascular area, and to determine the mass' relationship with the nearby vessels[34]. The enhancement intensity of the lesion is compared to that of the surrounding normal pancreatic tissue and is described as hyper-enhanced (more enhanced), iso-enhanced

(equally enhanced) or hypo-enhanced (less enhanced) accordingly[35]. In addition, the contrast uptake pattern, can be either homogenous or heterogenous[35]. CH-EUS for pancreatic mass evaluation has been assessed by Gincul *et al*[36] in a prospective multicentre study with results supporting its use in this setting. However, the recent European Society of Gastrointestinal Endoscopy (ESGE) Technical and Technology Review did not find CH-EUS superior to standard EUS for guiding tissue acquisition in solid pancreatic lesions[31]. The main features on CH-EUS that are reported to indicate pancreatic adenocarcinoma are hypoenhancement and heterogenous contrast distribution[36,37]. These characteristic features of pancreatic cancer were compared with the ones demonstrated in AIP cases when CH-EUS was used. In particular, a study by Cho *et al*[35] showed that hyperenhancement/isoenhancement in arterial phase and homogenous pattern of contrast distribution are significantly more common in focal AIP, while the presence of tortuous/non-regular internal vessels was found to be significantly more frequent in patients with pancreatic malignancy. Also, a review by Seicean *et al*[34] reported isoenhancement/hyperenhancement on CH-EUS as suggestive of AIP in agreement with the previous studies. Similar findings were demonstrated in a study by Dong *et al*[38], although in small numbers (10 AIP and 16 adenocarcinoma cases examined with CH-EUS), with all AIP cases showing hyperenhancement on CH-EUS, while all cancer cases were found as hypoenhanced on CH-EUS. The characteristic hypervascularization observed in AIP lesions and the surrounding tissue on CH-EUS may therefore help distinguishing them from cancerous lesions that are typically shown hypovascularized on CH-EUS[39].

Although these studies consistently point towards hypervascularity as a feature of AIP, the reported enhancement patterns demonstrate some variation between series. Possible explanation could be related to differences in contrast agent used, difference in equipment settings applied, and the arterial- *vs* late-phase timing of image acquisition, as well as relatively small sample sizes. Given that, and as with elastography, CH-EUS

findings should be considered as complementary information that can help raise or lower suspicion of AIP rather than a stand-alone diagnostic test.

TISSUE ACQUISITION IN AIP

Obtaining tissue samples is not only a critical step in the diagnostic workup of suspected AIP but it also plays a key role in ruling out pancreatic malignancy, which may present with similar clinical and radiological features. Sufficiency of sampling, the optimal site of sampling and the techniques involved have been a matter of discussion over recent years[18].

The role of papillary biopsies

Given that the papilla of Vater is more easily accessible, several studies investigated its role in the diagnostic investigation of AIP. To begin with, the endoscopic features of the papilla and their role in differentiating AIP from primary sclerosing cholangitis (PSC) were assessed in a study by Kubota *et al*[40]. It was indicated that a swollen papilla, along with the presence of IgG4+ plasma cells on immunostaining in biopsy samples, could help distinguishing the 2 entities. Similarly, a study by Kawakami *et al*[41] evaluated the utility of papillary and bile duct biopsies in distinguishing IgG4 related sclerosing cholangitis, widely associated with AIP, from PSC and pancreatobiliary malignancy cases. Yet again, biopsies from the papilla (as well as from bile ducts) were found bearing bigger number of IgG4+ plasma cells to a significant manner, when compared to the other 2 groups (PSC and cancer patients). The value of papillary biopsies in supporting the diagnosis of AIP has also been demonstrated in a study by Moon *et al*[42]. In spite of those promising data, it is important to interpret the presence of increased IgG4+ cells on papillary biopsies in the right clinical context, since as demonstrated in a study by Cebe *et al*[43], > 10 IgG4+ plasma cells in papillary or duodenal biopsies were also observed in coeliac disease cases, while increased IgG4+ cells were also seen in pancreatic malignancy

cases. Importantly, biopsies from the papilla or bile ducts do not help establish the diagnosis of AIP type 2[18].

EUS-guided tissue acquisition from the pancreas

EUS-guided tissue acquisition (EUS-TA) from pancreatic gland has been evaluated in the context of pancreatic cancer tissue diagnosis and was found to bear an acceptable diagnostic accuracy and safety profile[44]. Accordingly, several studies have investigated the role of EUS-TA in AIP diagnosis. EUS-TA techniques have been an ongoing field of innovation and active research over the previous years. The most recent published ESGE Technical and Technology review by Facciorusso *et al*[31] provided an up-to-date insight on this. In terms of EUS guiding the tissue acquisition, both B-mode and CH-EUS were found to be equally effective in several studies regarding solid pancreatic lesions[31,45,46]. With regards to the needle types, different options include the historically available fine-needle aspiration (FNA) and the fine-needle biopsy (FNB) needles, with the latter consisting of two categories, the reverse-bevel FNB and the end-cutting FNBs[31]. The preferred needle option has been a matter of debate and was assessed in several studies and meta-analyses as outlined in the following paragraphs.

FNA, was considered for many years the benchmark for tissue acquisition, until the introduction of the FNB needles[47]. Structural limitations of the FNA needles did not allow for collection of core biopsy samples with retained cellular architecture[47]. This drawback is especially significant when the aim of the procedure is to diagnose suspected AIP and exclude pancreatic malignancy[31]. In particular, the histopathological features that, based on ICDC criteria, help establish the diagnosis of either AIP type 1 or type 2, are generally not present in needle aspiration (cytology) specimens, rendering the value of FNA in this setting problematic[48]. To overcome this limitation, FNB needles were designed, that are able to maintain the tissue's structural integrity along with these histological features that could support the AIP diagnosis[49]. Despite the fact that the

initially presented reverse-bevel FNBs were not found superior in terms of diagnostic accuracy and adequate sample acquisition in comparison to FNA needles[50,51], the next generation of FNB needles, known as end-cutting FNBs, showed better outcomes[52]. Particularly, in a meta-analysis of solid pancreatic masses (not specific to AIP) by Gkolfakis *et al*[52], third generation FNB needles, and more specifically the 22G fork-tip and Franseen type needles, were found to bear better accuracy and sample adequacy, compared to FNA and reverse-bevel FNBs. The superiority of the end-cutting FNBs against the other EUS-TA needle options for the biopsy of solid pancreatic masses, is also incorporated into the recently published ESGE Technical and Technology review[31]. A role for FNA is still reserved in this context, if rapid on-site evaluation (ROSE) is readily available and the standard of local practice[31].

The utility of the end-cutting FNB needles has been specifically evaluated in AIP cases, by a number of studies. Accordingly, in a study by Ishikawa *et al*[53] the 22G Franseen type needle was found to have good detection rates of the histopathological features for AIP. Favourable outcomes regarding the usefulness of both Franseen and fork-tip needles in the diagnostic workup of AIP type 1, especially regarding successful sampling, diagnostic biopsies and histological diagnosis rate, were demonstrated in several studies in recent years[54-56]. A systematic review and meta-analysis by Facciorusso *et al*[48] included 631 AIP patients, and estimated the diagnostic accuracy of EUS-TA, which was found modest, measuring 54.7%, with FNB accuracy being 63%, significantly greater than that of FNA which was estimated at 45.7%. In the recent ESGE Technical and Technology review, an updated meta-analysis estimated the overall diagnostic accuracy of EUS-FNB in AIP cases to 75%[31]. This improvement over time likely reflects several concurrent developments rather than a single technical advance, including the progressive shift from reverse-bevel to end-cutting FNB needles, the more consistent incorporation of on-site sample evaluation, and the likely greater clinical awareness of AIP. When the different generations of FNB needles were compared, the end-cutting FNBs demonstrated

diagnostic accuracy of 80%, significantly increased compared to that of reverse-bevel FNB measuring 49%[31]. Therefore, the suggestion from the panel is for end-cutting FNBs to be preferred over other generations of FNBs and FNA needles, in suspected AIP cases, even though this is a conditional recommendation based on very low-quality evidence[31].

EUS-TA adverse events: EUS-TA and in particular EUS-FNB adverse events were evaluated in a recent systematic review and meta-analysis by Pan *et al*[57], that included 9303 patients undergoing EUS-FNB for upper gastrointestinal tract lesions. In this study, which was not specific to AIP, the overall incidence of adverse events was 1.8% and was 2.6% for pancreatic lesions, while pancreatitis accounted for approximately one quarter of all adverse events. Of note, no deaths associated with the procedure were reported.

With regard to safety profile of EUS-TA in AIP cases, a meta-analysis by Facciorusso *et al*[48] confirmed its adequate safety profile, with only a small number of patients experiencing adverse events, which were mild and consisted mainly of acute pancreatitis in less than 1% of patients.

Assessment of biopsy sample adequacy

Given that the acquisition of an adequate biopsy sample is crucial in a pancreatic lesion's diagnostic workup, especially where a pancreatic cancer remains to be excluded, the concept of ROSE of the sample was introduced. In ROSE, the sample is evaluated microscopically on-site by a histopathologist, confirming that the lesion was biopsied, and accordingly allowing for further biopsies/passes if needed[58]. This assessment is recommended only if EUS-FNA is performed and is not regarded necessary when end-cutting FNB needles are used[31,59]. An alternative technique for FNB to address on-site evaluation is the macroscopic on-site evaluation (MOSE), which consists of a macroscopic assessment of the biopsy sample placed on a specimen glass slide. Sample adequacy is

based on the detection of a white or yellow core that is ≥ 4 mm in size[60]. Less needle passes are needed to determine the diagnosis, when MOSE is used alongside EUS-FNB[61]. A more straightforward and accessible on-site sample evaluation can be achieved with the visual on-site evaluation, which enables the assessment of the sample directly into the formalin vial. The detection of red-mixed specimen was found to correlate with an adequate biopsy sample[62]. Therefore, the ESGE Technical and Technology review recommended the use of MOSE, along with EUS-FNB, while more data are awaited before proceeding with recommendations regarding visual on-site evaluation[31]. Of note, these on-site evaluation methods have been studied in solid pancreatic lesions in general, whereas AIP-specific studies remain lacking.

EUS-TA in focal and diffuse pancreatic enlargement

As detailed above, the importance of EUS-guided biopsy in excluding pancreatic malignancy, as well as differentiating AIP type 1 from AIP type 2 and, along with other findings (serology, imaging, clinical), supporting the diagnosis, is well established.

It is especially highlighted by the 2018 Japanese criteria for AIP, that steroid trial may be considered only once pancreatic cancer has been ruled out[63]. In that direction, EUS-TA is considered a useful tool, but using imaging studies in this process is equally important, given that the lack of malignant cells in histopathology alone is not considered sufficient cancer exclusion criterion[63]. Moreover, even though response to steroids is likely indicative of AIP, it does not rule out malignancy. Accordingly, an amendment of the Japanese guidelines pointed out that especially in mass-forming lesions, an exclusion of malignancy employing EUS-TA or endoscopic retrograde cholangiopancreatography (ERCP) with biopsy/brushings should precede a steroid trial[64].

With regards to AIP diagnosis, several studies examined the role of EUS-TA in cases with diffuse pancreatic enlargement and in cases with focal swelling. In a study by Noguchi *et al*[65], a population of 53 patients, containing 22 patients with diffuse and 31

patients with focal swelling, was assessed for EUS-TA role in affecting the diagnosis. In the group with diffuse enlargement, EUS-tissue acquisition with either FNA or FNB, aimed for head of pancreas in 32%, body of pancreas in 50% and tail of pancreas in 18% of cases. Of note, EUS-TA in the diffuse enlargement group did not affect the diagnosis, that was already established through imaging, serology and OOI criteria[65]. On the contrary, EUS-tissue acquisition changed the diagnosis in 38.7% of the group with focal enlargement of the pancreas[65]. In accordance with this, a study by Notohara *et al*[66] demonstrated that histopathology contributed to a definitive diagnosis in 1 out of 28 patients with diffuse pancreatic enlargement, compared to 25 out of 45 patients (55.6% according to the Japanese criteria; 33.3% according to the ICDC) with focal pancreatic enlargement. Therefore, EUS-tissue acquisition is underscored as more beneficial in cases with focal enlargement.

With respect to the modality used to obtain tissue in cases when diagnosis cannot be established without histopathology, the Japanese guidelines recently recommended EUS-TA (FNA or FNB), while papillary biopsies could be added in cases that ERCP was carried out[64].

ADVANCES IN ARTIFICIAL INTELLIGENCE-ALGORITHMS FOR EUS

Despite the crucial role that EUS plays in AIP diagnosis, inter-observer variability based on the locally available expertise, can affect outcomes and lead to misdiagnosis[67]. In recent years, subject of significant interest in the attempt to reduce this phenomenon and enhance the diagnosis of AIP in general, is artificial intelligence (AI). AI- algorithms have started to emerge, regarding EUS images interpretation and tissue acquisition[68].

In a study by Kuwahara *et al*[69], an AI diagnostic model using EUS images was presented in order to distinguish pancreatic cancer from other pancreatic lesions. This model interestingly showed 0.94 sensitivity and 0.82 specificity for pancreatic malignancy diagnosis while a 0.73 sensitivity for AIP was demonstrated[69]. Similarly, a study by

Marya *et al*[70] was designed to develop an EUS-based model that could distinguish AIP from normal pancreas, chronic pancreatitis and pancreatic cancer. It was found that this model could accurately assist in differentiating AIP from the other included benign and malignant conditions, with high sensitivity and specificity, measuring 90% and 85% respectively[70]. In a more detailed fashion, the sensitivity and specificity for differentiating AIP from normal pancreas was 99% and 98% respectively, for distinguishing AIP from pancreatic malignancy was 90% and 93% respectively and for distinguishing AIP from chronic pancreatitis was 94% and 71% respectively[70]. A meta-analysis by Dhali *et al*[71] further assessed the value of AI-assisted EUS and revealed increased accuracy of AI models in diagnosing and distinguishing pancreatic masses in general, rather than AIP specifically.

While these diagnostic performance figures are encouraging, they call for more critical methodological evaluation than diagnostic accuracy alone. Most of these models, including the ones developed by Kuwahara *et al*[69] and Marya *et al*[70], were trained and validated using retrospective, single-centre image datasets containing relatively small numbers of confirmed AIP cases, while AIP cases represent a minority group within a larger cohort of different pancreatic lesions. This observed imbalance may limit confidence in the reported sensitivity and specificity for AIP. In addition to this, direct comparison with the diagnostic performance of experienced hepatopancreatobiliary (HPB) endoscopists is generally lacking, while none of the models discussed have yet been prospectively validated and evaluated in real-world clinical practice across different centres and different endoscopists. Overall, current evidence of the literature supports these AI tools as proof-of-concept diagnostic aids rather than a validated instrument ready for routine clinical decision-making.

Additionally, AI was also assessed in the setting of tissue acquisition. Given that ROSE is not available in all the hospitals that are still using FNA needles, mainly due to costs and lack of histopathologists, an AI model to assist ROSE (ROSE-AI) was designed in an

attempt to overcome this problem[72]. This AI model showed promising results in enhancing EUS-FNA accuracy and was proposed as a potential alternative to conventional ROSE[72], although it should be noted that it was developed for the detection of cancer cells and has not yet been evaluated in AIP cases. Nevertheless, in an era in which FNB is the standard technique for tissue acquisition, it is anticipated that AI will be applied primarily to enhance image interpretation rather than to replace core biopsy-based diagnosis.

THE ROLE OF IGG4 MULTIDISCIPLINARY TEAM MEETINGS IN CLINICAL DECISION MAKING

Given the diagnostic challenges posed by IgG4-RD, the implementation of dedicated IgG4 multidisciplinary team (MDT) meetings is increasingly used as an approach to address these complexities. A holistic approach to diagnosis and management involves shared assessment and decision-making by a panel of specialists in HPB endoscopy, hepatology, rheumatology, radiology, cardiology, nephrology, and histopathology.

To this end, a United Kingdom National specialist IgG4-RD MDT has been established in the Oxford University Hospitals. This monthly meeting aims to establish a diagnosis of IgG4-RD in complex cases, formulate a concise management plan, assess treatment response and need to escalate treatment, and facilitate recruitment into research studies[73]. Moreover, this multidisciplinary approach helps ascertain the need for tissue acquisition and the most appropriate approach. The IgG4 pathway presented in this review, reflects our institutional experience of running a United Kingdom National multi-centre IgG4-RD MDT and could therefore be considered as an illustrative-exemplar of practice rather than a model formally mandated by published guidelines. Of note, existing recommendations support the principle of multidisciplinary input but do not describe a specific meeting structure, specialty composition or referral pathway. Indeed, high-quality evidence comparing patient outcomes with a dedicated MDT *vs* standard

specialist referral remain lacking, and the published experience of our IgG4-RD MDT, in which management was changed in 74% of the patients discussed, likely reflects process outcomes rather than proven improvements in patient outcomes[73].

The accumulated experience and multidisciplinary approach within dedicated MDTs have been valuable in the management of IgG4-related disease[73], and their possible wider adoption may support patient-centred care, although this view is currently based largely on national multi-centre experience rather than comparative outcome data.

A comprehensive approach incorporating IgG4 MDT discussion into the implementation of EUS assessment and tissue acquisition in the diagnostic workup of AIP is illustrated in Figure 1, as a United Kingdom National MDT example rather than a validated or universally applicable pathway.

Figure 1 summarises the proposed algorithm, which is discussed here to provide narrative support for the reader. Following clinical and cross-sectional imaging suspicion of AIP, the early implementation of case-discussion in an IgG4-MDT meeting, can help guide management and guide the need for EUS evaluation. If EUS is recommended, it is used both to characterise pancreatic morphology, using B-mode, elastographic and, where available, contrast-enhanced features, and to obtain tissue *via* EUS-TA, preferably with an end-cutting FNB needle accompanied by on-site evaluation of tissue sufficiency. Papillary biopsy may be added when ERCP is performed for biliary indication. The resulting histological, serological and imaging will inform the IgG4-MDT discussion so that a management and treatment plan can be agreed. This proposed algorithm is intended as a practical illustration of how the tools discussed in this review may be integrated into everyday practice, rather than as an already validated pathway. Accordingly, it should be noted that the pathway should be adapted to local expertise and resources, whereas the EUS elastography and CH-EUS features shown in Figure 1 should be regarded as supportive findings only.

GLOBAL ACCESSIBILITY OF EMERGING TECHNIQUES

Cost-effectiveness and global accessibility of the emerging modalities discussed in this review, warrant explicit consideration. Advanced EUS techniques, including CH-EUS, EUS-elastography, and AI-assisted interpretation require specific equipment, while ROSE require the availability and on-site presence of a histopathologist. With limited resources being an issue in multiple health care systems, universal availability is a point in question. Taking this into consideration, a pragmatic interpretation approach to the diagnostic algorithm proposed here should be that this is regarded as aspirational in healthcare settings without access to these techniques. To this accord, conventional B-mode EUS tissue acquisition, supported where possible by MOSE, remains a reasonable and pragmatic first step.

LIMITATIONS AND FUTURE DIRECTIONS

Several important gaps remain in the current literature on the utilisation of EUS for AIP management. First, prospective, multicentre studies are lacking across many of the domains discussed in this review, including EUS-elastography, CH-EUS and AI-based diagnostic models, with most of which relying on retrospective, single-centre studies. Second, there is no widely accepted standardisation of EUS-elastography thresholds or CH-EUS enhancement criteria, limiting comparability between centres. Third, there is a lack of consensus on the optimal EUS-TA sampling site for suspected AIP, especially in diffuse pancreatic enlargement cases. Fourth, validation of the AI models described above and head-to-head comparison with expert HPB endoscopists, is still awaited. Fifth, much of the evidence on needle choice, on-site biopsy sample evaluation, CH-EUS features and EUS-elastography features derives from studies of solid pancreatic masses in general rather than from dedicated AIP-specific series.

Future research priorities could therefore include multicentre prospective validation of the diagnostic tools discussed, standardisation of imaging and elastography criteria,

optimisation of EUS-TA sampling strategies specifically for AIP, validation of AI models across different centres, evaluation of AI models performance in real-world clinical practice, and assessment of how these emerging modalities can best be integrated into multidisciplinary diagnostic pathways.

CONCLUSION

In summary, EUS is recognised as an increasingly valuable component of the diagnostic pathway for AIP, complementing data acquired from cross-sectional imaging, serology and multidisciplinary assessment in the important task of excluding pancreatic malignancy and establishing a definitive diagnosis of AIP. Techniques such as EUS-elastography and CH-EUS may provide complementary diagnostic information to the conventional EUS features, although the supporting evidence remains somewhat heterogeneous and is currently drawn largely from small single-centre studies. EUS-TA and particularly EUS-FNB using end-cutting needles, seems to have improved the diagnostic yield of tissue acquisition, with specific value in patients presenting with focal pancreatic enlargement. AI has shown promising proof-of-concept performance for supporting EUS image interpretation, but external validation and real-world evaluation is needed before its clinical utility can be considered established. IgG4-MDT evaluation of suspected AIP cases, integrating imaging, histological and serological data, is valuable for establishing a confident diagnosis and guiding case management, although the specific structure of this collaboration will understandably vary between centres. Further, prospective, multicentre studies, are required before these emerging techniques can be more firmly embedded in everyday clinical practice.

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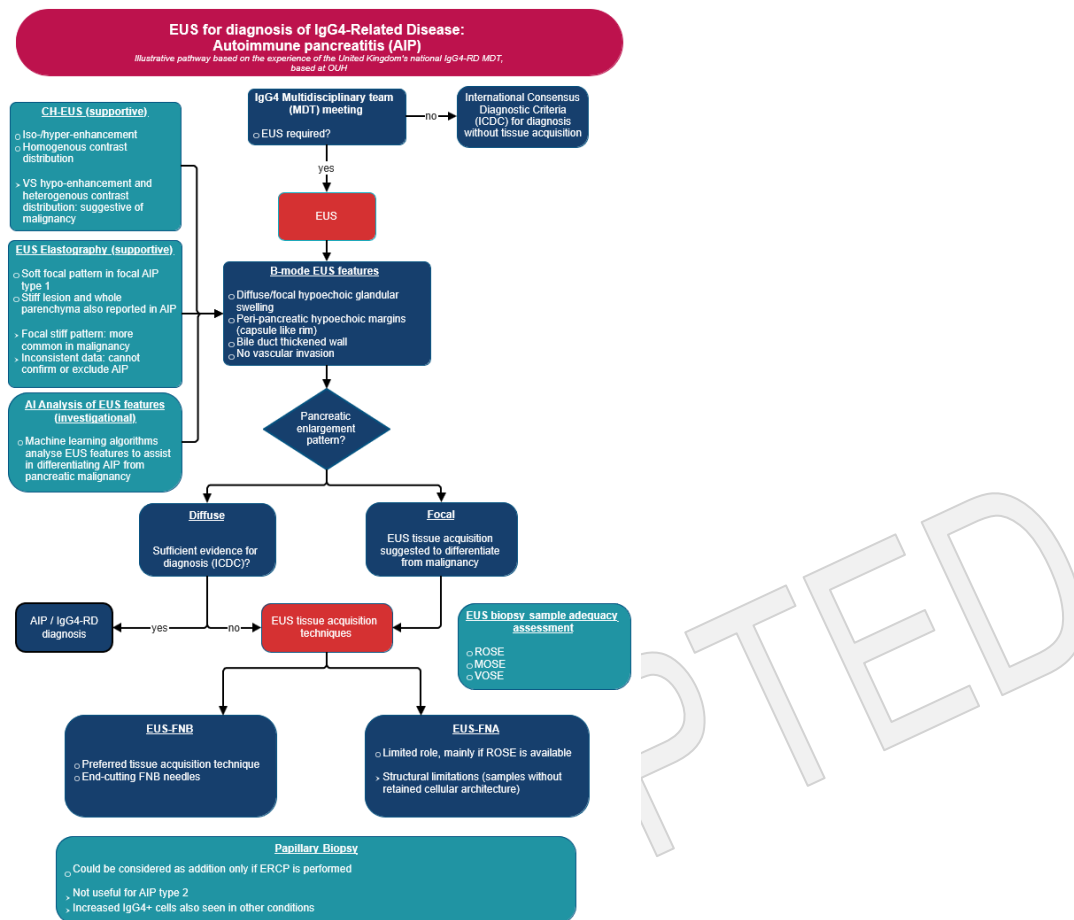


Figure 1 Illustrative pathway for incorporating endoscopic ultrasound into the diagnostic evaluation of autoimmune pancreatitis. The demonstrated pathway is proposed by the authors, based on the United Kingdom National multicentre multidisciplinary team meeting experience taking place in Oxford University Hospitals, along with the literature discussed in this review. It is not a formally validated clinical algorithm or a consensus guideline. EUS: Endoscopic ultrasound AIP: Autoimmune pancreatitis; MDT: Multidisciplinary team; OUH: Oxford University Hospitals; IgG4: Immunoglobulin G subclass 4; CH-EUS: Contrast-enhanced harmonic endoscopic ultrasound; VS: Venous phase; ICDC: International Consensus Diagnostic Criteria; ROSE: Rapid on-site evaluation; MOSE: Macroscopic on-site evaluation; VOSE: Visual

on-site evaluation; FNB: Fine-needle biopsy; FNA: Fine-needle aspiration; ERCP: Endoscopic retrograde cholangiopancreatography.

ACCEPTED