# Diagnosis of Indeterminate Biliary Strictures using Ultrasonography Endoscope

**Mostafa Moaz Mostafa, Hamed Mohammad Soliman, Amira Mohammad Soliman, Ahmed Atya Abdelmoaty**

Tropical Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

**Corresponding author:** Mostafa Moaz Mostafa

E-mail: mostafamoaz3010@gmail.com, mmoaz@medicine.zu.edu.eg

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**Abstract**

**Background: Previously, the decision to operate has traditionally been made on the basis of clinical history and cholangiographic appearance of the stricture and sometimes empiric resection was necessary to differentiate benign and malignant strictures. However, determining the cause of a stricture on the basis of morphologic features and brush cytology is unreliable. EUS provides a high-resolution imaging modality that has evolved not only as a diagnostic tool but also as a therapeutic and interventional procedure. Since EUS is now the first choice in screening for small pancreatic tumors that cannot be detected by other imaging modalities and is not associated with ERCP-related complications, its utility for differentiating malignant and benign biliary strictures thus warrants more discussion. EUS provides the ability to identify a mass lesion not detected by other imaging modalities and enables high-definition imaging of stricture morphology. In addition, it facilitates staging by assessing regional lymphadenopathy and vascular involvement. Tissue acquisition using EUS-guided fine-needle aspiration (EUS-FNA) can also be performed.**

**Keywords: Ultrasonography Endoscope, Indeterminate Biliary Strictures**

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## Introduction:

Previously, the decision to operate has traditionally been made on the basis of clinical history and cholangiographic appearance of the stricture and sometimes empiric resection was necessary to differentiate benign and malignant strictures **(Lee et al., 2004).** However, determining the cause of a stricture on the basis of morphologic features and brush cytology is unreliable **(Fogel et al., 2006).** .

EUS provides a high-resolution imaging modality that has evolved not only as a diagnostic tool but also as a therapeutic and interventional procedure **(Bhutani, 2000).** Since EUS is now the first choice in screening for small pancreatic tumors that cannot be detected by other imaging modalities and is not associated with ERCP-related complications, its utility for differentiating malignant and benign biliary strictures thus warrants more discussion **(Brand et al., 2007).**

EUS provides the ability to identify a mass lesion not detected by other imaging modalities and enables high-definition imaging of stricture morphology. In addition, it facilitates staging by assessing regional lymphadenopathy and vascular involvement. Tissue acquisition using EUS-guided fine-needle aspiration (EUS-FNA) can also be performed **(Yang et al., 2016).**

EUS and EUS-FNA have several advantages in the evaluation of biliary strictures. The procedure can evaluate the pancreas for the presence of a mass or changes of chronic pancreatitis, both of which can cause biliary strictures. EUS-FNA can also be taken during the same procedure from mass or regional lymphadenopathy for a definitive diagnosis **(DeWitt et al., 2006).**

In the evaluation of biliary strictures, the presence of biliary stents may lead to thickening and asymmetry of the bile duct wall. These stent-related findings must be recognized at the time of EUS **(Byrne et al., 2004).**

**Endoscopic Ultrasonography and Pancreatic Neoplasms:**

EUS is the most sensitive non-operative imaging technique for the detection of benign or malignant pancreatic lesions with reported sensitivities of over 95% in most studies. This excellent sensitivity has provided the rationale for its use (along with MRI) in screening high-risk individuals for pancreatic duct adenocarcinoma (PDAC). EUS is particularly useful for identification of small tumors (≤20 mm in diameter) that have been undetected by other imaging modalities **(Al-Haddad and DeWitt, 2011).**

EUS-FNA has become an essential tool for the evaluation of pancreatic lesions. Since its first use in the early 1990s, it has evolved into an efficient technique with good safety profile and high diagnostic accuracy ranging 80%-90% **(Panic and Larghi, 2014).** EUS may detect and sample metastatic liver masses, ascites, or distant lymph nodes missed by other imaging studies and therefore meticulous search for these lesions should be carried out during these exams **(DeWitt et al., 2007).**

An analysis of 20 studies and 726 cases of pancreatic cancer showed that EUS for T1-2 staging has a sensitivity and specificity of 72% and 90%, respectively. Sensitivity and specificity for T3-4 staging is 90% and 72%, respectively. The sensitivity and specificity values for nodal staging (62% and 74%, respectively) are lower than the values for vascular invasion (87% and 92%, respectively) **(Li et al., 2014).**The role of EUS in staging is felt to be complementary to CT, providing additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes **(Wang et al., 2013).**

In particular, EUS may provide assessment of certain types of vascular invasion. While the accuracy of EUS in assessing the involvement of certain veins (eg, portal vein) is high, the technique is less accurate in imaging tumor invasion of the superior mesentric artery **(Buchs et al., 2010)**.

EUS and multidetector CT are equivalent at determining surgical resectability of PDAC. Although the TNM (tumor node metastasis) staging system is widely used for staging of PDAC, dividing these patients into resectable, borderline resectable, locally advanced, and metastatic categories is more clinically useful **( Dewitt et al., 2006)**.

Resectable cancers have no vascular or regional spread, which would contraindicate surgery. Borderline cancers have regional spread into vessels (i.e., portal vein) or other organs (i.e., stomach), which would make surgery difficult but not impossible (i.e., with vein removal and reconstruction or partial gastrectomy, respectively). Locally invasive cancers are not metastatic but have invasion into structures (e.g., celiac artery), which make curative surgery impossible. Metastatic tumors are surgically incurable because of the spread to distant sites (i.e., lung, liver) **(Nawaz et al., 2013)**.

**Table (1):** Criteria defining resectability status **(Al-Hawary et al., 2014)**

| Resectability Status | Arterial | Venous |
|---|---|---|
| **Resectable** | No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). | No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180°contact without vein contour irregularity |
| **Borderline Resectable** | <u>Pancreatic head /uncinate process:</u><br>• Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.<br>• Solid tumor contact with the SMA of ≤180°<br>• Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. | • Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.<br>• Solid tumor contact with the inferior vena cava (IVC). |

| | | |
|---|---|---|
| | **Pancreatic body/tail:**<br>• Solid tumor contact with the CA of ≤180°<br>• Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery [some members prefer this criteria to be in the unresectable category]. | |
| **Unresectable** | • Distant metastasis (including non-regional lymph node metastasis)<br>**Head/uncinate process:**<br>• Solid tumor contact with SMA >180°<br>• Solid tumor contact with the CA >180°<br>• Solid tumor contact with the first jejunal SMA branch<br>**Body and tail:**<br>• Solid tumor contact of >180° with the SMA or CA<br>• Solid tumor contact with the CA and aortic involvement | **Head/uncinate process:**<br>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)<br>• Contact with most proximal draining jejunal branch into SMV<br>**Body and tail:**<br>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) |

**Endoscopic ultrasonography and ampullary Neoplasms:**

The prognosis of ampullary carcinoma has been reported to be more favorable than that of pancreatic cancer **(Tierney et al., 2001).** In one study, the 5-year survival after resection of ampullary cancer and pancreatic head ductal cancer was 38% and 16%, respectively. **(Klempnauer et al., 1999)** .

Midwinter et al, evaluated the findings from spiral CT and EUS in 34 patients with suspected pancreatic and ampullary tumors, and found that the diagnostic accuracy of EUS Vs CT was 97% Vs 76% **(Midwinter et al., 1999).** Also, Shoup et al . also demonstrated that EUS is more accurate than CT in detecting periampullary tumors < 2 cm (90% vs 70%) **(Shoup et al., 2000)**. Thus, EUS shows superiority over CT in detecting periampullary tumors < 2–3 cm in diameter **(Nguyen et al., 2002).** node metastasis. Non resectability was accurately assessed on the basis of vascular involvement. The overall accuracy in tumor staging and nodal staging for ampullary carcinomas

was 84.4%, 63% respectively. In diagnosing pancreatic invasion, EUS had an accuracy of 86%, sensitivity of 83% and specificity of 87% **(Rathod et al., 2002).**

The importance of EUS or other imaging modalities in defining vascular invasion by pancreatic and major duodenal papilla malignancies is based on the principal of surgical resectability. Patients with vascular invasion of peri pancreatic vessels or distant metastasis are not candidates for curative resection. Accurate preoperative staging is critical in selecting patients for attempted curative resection versus palliative interventions. In addition to accurately predict staging and resectability of ampullary and pancreatic tumors, EUS findings correlate well with prognosis **(Williams and Hoffman, 1999).**

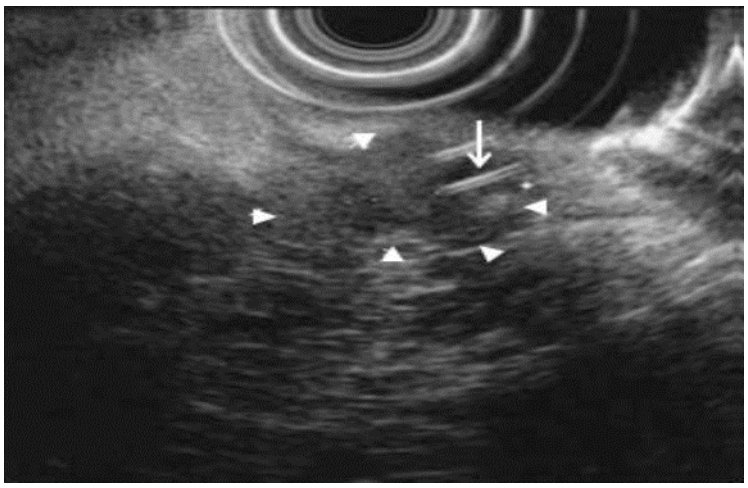

**Figure (1):**

Radial endoscopic ultrasonography image of ampullary carcinoma (►) seen around a biliary stent (→). The tumor appears hypoechoic and the image is consistent with infiltration into the pancreatic head (**Yusuf and Bhutani, 2004).**

**Endoscopic Ultrasonography and Cholangiocarcinoma :**

EUS allows detailed examination of the extra hepatic biliary tree because of the proximity of the US probe in the proximal duodenum to the bile duct. Examination of the bile duct is typically started with the echo endoscope situated at the ampulla. By slowly withdrawing and rotating the echo endoscope toward the pylorus region, the entire bile duct can be examined. A second position to examine the bile ducts is a long endoscope position in the duodenal bulb, where it is often possible to obtain a longitudinal image of the duct. Both the bile duct bifurcation into the left and right main intrahepatic ducts and bile duct insertion into the ampulla should be identified to ensure complete examination of the extra hepatic bile duct. Bile duct masses typically appear as hypo-echoic lesions on EUS **(Glesson et al., 2008).**

The relationship of the mass to the hepatic parenchyma, portal vasculature, and hepatic arteries should be scrutinized to stage the tumor and assess for resectability **(Krishna et al., 2007).**

Endosonographic staging of cholangiocarcinoma is based on the tumor, nodes, metastasis system. Patients with suspected cholangiocarcinoma should preferably have a confirmatory cytopathologic diagnosis before curative radical resection is attempted **(Eloubeidi et al., 2004).**

The difficulty is amplified when there is an attempt to discern malignant from non malignant strictures in patients with primary sclerosing cholangitis, because this affects transplantation decisions. The reported sensitivity of EUS FNA for the diagnosis of cholangiocarcinoma in patients with indeterminate extrahepatic biliary strictures ranges between 43% and 89%, with most studies reporting sensitivities greater than 70%. A definite mass is seen on radiologic imaging in only a third of patients with extrahepatic cholangiocarcinoma In contrast, most studies reported visualization of biliary mass lesions during EUS in the majority of patients **(Eloubeidi et al., 2004).**

EUS FNA is, thus, feasible in most cases because a mass can be visualized. Occasionally, bile duct wall thickening rather than a mass is visualized by EUS. In these instances, careful FNA of the thickened duct wall can be attempted by using a 22-gauge or a 25-gauge FNA needle. Two clinical aspects may impact the sensitivity of EUS FNA of indeterminate extrahepatic biliary strictures: location of stricture (proximal vs distal) and the presence of a bile duct stent. Mohamad nejad et al compared sensitivity of EUS-FNA of proximal and distal cholangiocarcinoma and found significantly lower sensitivity for proximal tumors (59% vs 81%; P = .04, respectively) **(Mohamadnejad et al., 2011)**.

This could be explained by the relative ease of visualizing and sampling distal bile duct lesions. In contrast, proximal lesions are further from the tip of the echoendoscope and are closer to the liver parenchyma, rendering their diagnosis and sampling more challenging. Although the presence of a bile duct stent could provide a point of reference and may facilitate identification of a bile duct tumor, the stent itself may produce significant acoustic shadowing that interferes with sonographic imaging of the tumor. In addition, the presence of the stent through a bile duct tumor limits access to and FNA of the contralateral side of the tumor **(Fusaroli et al., 2007).** .

From a practical standpoint, most patients who present for EUS-FNA for suspected cholangiocarcinoma would have undergone ERCP with biliary stenting for diagnosis (ie, brushing) and treatment of biliary obstruction (ie, stenting). Therefore, most patients will have a biliary stent in place. Whenever feasible, EUS-FNA should be performed immediately before placement of biliary stents to improve diagnostic and staging accuracy of suspected biliary tumors and eliminate the subsequent risk of cholangitis arising from inadvertently contaminating the obstructed biliary system during FNA (**Rosen et al., 2010)**.

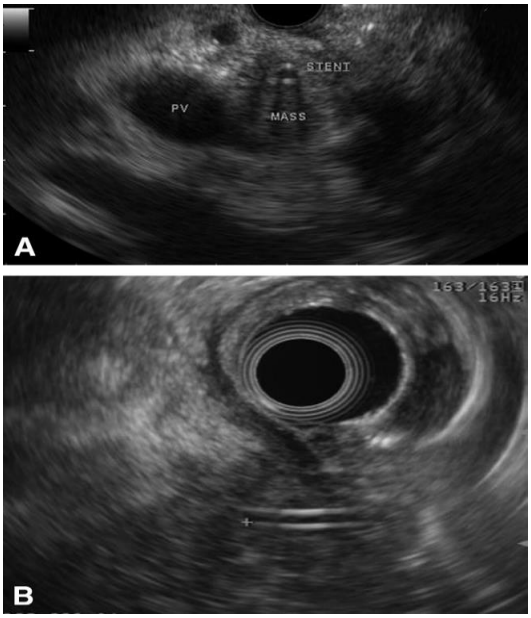


**Figure (2): A,** EUS revealing a small distal bile duct mass with a stent seen in the bile duct. The mass abuts the portal vein. The superior mesenteric artery is not involved and is seen posterior to the portal vein. **B,** EUS demonstrating a hypoechoic distal bile duct mass invading the duodenal wall. PV, portal vein. **(Khashab et al., 2012)**

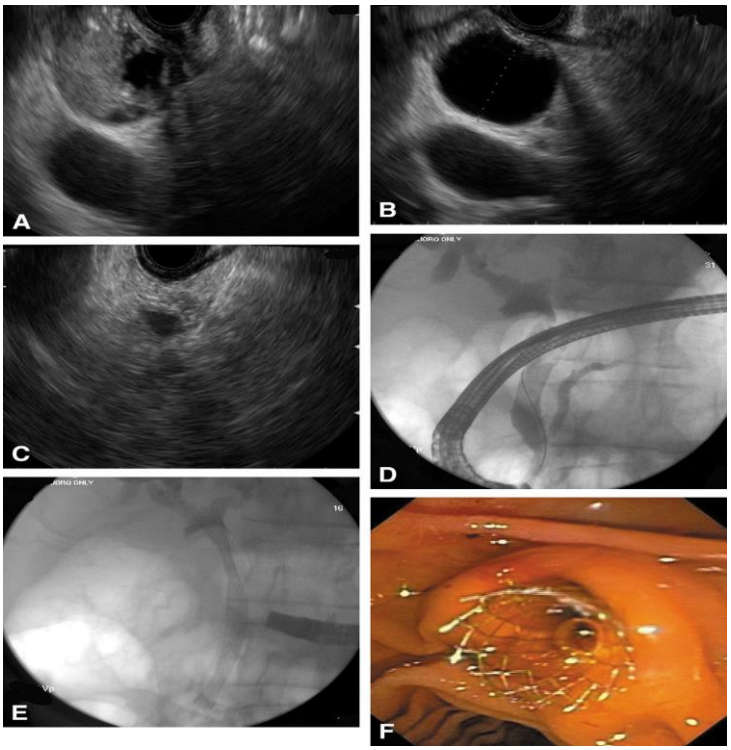


**Figure (3): A,** EUS showing a bile duct mass that was missed by a CT scan and MRI. **B,** Biliary dilation was present proximal to the stenosis. **C,** EUS-FNA was performed and was diagnostic of cholangiocarcinoma. **D,** ERC was performed during the same session, and cholangiography revealed a distal biliary stricture. **E, F,** A self-expandable metal biliary stent was placed. **(Hoffman et al., 2008)**

**Endoscopic Ultrasound in The Diagnosis of Chronic Pancreatitis :**

EUS has the ability to produce high-resolution ultrasonography images of the pancreas due to the proximity of the transducer to the gland, avoiding interference by air in the intestine. EUS diagnosis of CP is based on specific criteria that have been described by the International Working Group for Minimum Standard Terminology in Gastrointestinal Endoscopy **(Aabakken et al., 2009).** These comprise five parenchymal criteria (hyperechoic foci, hyperechoic strands, parenchymal lobularity, cysts, calcifications) and five ductal criteria (pancreatic duct dilation, pancreatic duct irregularity, hyperechoic pancreatic duct walls, visible pancreatic side branches, intraductal calcifications). .

The number of criteria that is needed to establish the diagnosis of CP and the relative weight of each criterion has been a matter of debate for several years. The first attempts to create an integrated evaluation of EUS based CP findings simply used the sum of positive criteria and defined EUS findings consistent with CP as a certain minimum number of positive criteria **(Varadarajulu et al., 2007).** .

In an attempt to allow for differentiated weighting of CP criteria and to harmonize EUS based diagnosis of CP, the Rosemont classification was published in 2009. The Rosemont classification is a definition of EUS based CP criteria produced by a group of endo sonography experts at an international consensus conference. Ductal and parenchymal EUS findings are divided into major A, major B and minor criteria. As opposed to the previous simple counting of criteria, the Rosemont classification gives different weight to different findings. Based on the number and character of positive EUS criteria, EUS evaluation is classified as “consistent with CP”, “suggestive of CP”, “indeterminate for CP”, or “normal”. This system agrees with the standard classification in 74% of cases, increasing to 84% when “suggestive of CP” was included as CP **(Catalano et al., 2009).**

One of the most important weaknesses of EUS in the diagnosis of CP is concern about poor interobserver agreement. Interobserver agreement differs between EUS criteria. Duct dilation and lobularity was demonstrated to have the highest agreement in one study **(Wallace et a., 2001)** while hyperechoic strands and parenchymal cysts were found to have the highest agreement in another study **(Gardner et al., 2012).**

Inter observer agreement for standard EUS classification versus Rosemont classification for CP has been evaluated in a multicenter study. Fourteen experts evaluated 50-recorded videos using the standard EUS criteria (CP diagnosis if ≥ 3) and the Rosemont classification (considering “suggestive of CP” and “consistent with CP” as positive findings). Kappa score for inter-observer agreement on the Rosemont classification was 0.65(substantial aggreement), and the kappa score for standard classification was 0.54(moderate aggreement). Best agreement was noted for calcifications (standard scoring), pancreatic duct calcifications (Rosemont classification) and pancreatic duct dilation (both systems).The poorest agreement was seen for lobularity without

honeycombing (Rosemont classification). Patients were correctly classified as definite CP in 91.2% of cases according to standard scoring and 83.5% to Rosemont classification; as mild CP in 50% according to standard scoring and 42.9% according to Rosemont classification; and not CP in 83.3% and 95.2% of cases respectively **(Stevens et al., 2010)**.

**A** **B**

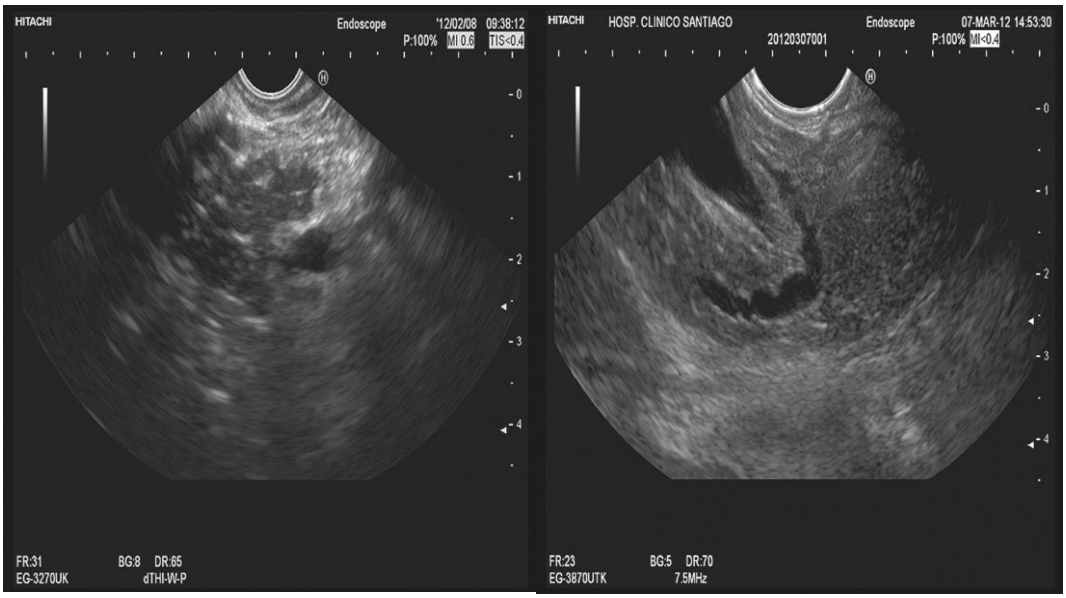


Fig (4): Different EUS criteria in a patient diagnosed of chronic pancreatitis (parenchymal: Lobularity, strands and foci [A]; ductal: Irregular MPD with hyperchoic wall [B]) **(Iglesias-Garcia et al., 2011)**.

**Autoimmune pancreatitis (AIP)** is a rare form of chronic pancreatitis characterized by abundant lymphoplasmacytic infiltration, interstitial fibrosis, obliterative venulitis, and elevated serum levels of IgG4 **(Cheuk and Chan, 2010).**

About 33-41 % of AIP present as a mass-like focal lesion that share clinical, laboratory, and radiologic features with pancreatic ductal adenocarcinoma (PDAC). Differentiation of these entities can sometimes be difficult in clinical practice. Approximately one-third of patients with tumefactive chronic pancreatitis undergo pancreatic resection because PDAC is suspected on preoperative studies. However, AIP usually improves after a short course of corticosteroid use without any surgical treatment **(Raimondi et al., 2010).**

Therefore, accurate preoperative differentiation between mass-forming AIP and PDAC is important. Several radiologic studies have been performed for differentiating mass-forming AIP and PDAC, but most of them have focused on morphologic findings, and debate and difficulties persist regarding differential diagnosis **(Graziani et al., 2014).**

- **Classification of AIP**

Type 1 AIP

Type 1 AIP is histologically characterized as lymphoplasmacytic sclerosing pancreatitis and is often associated with: (1) abundant lymphoplasmacytic infiltration with IgG4-positive cells > 10 cells/high power field (HPF) ; (2) storiform fibrosis; and (3) obliterative phlebitis. Destructive changes to the ducts and acini caused by infiltrating granulocytes are typically absent **(Umehara et al., 2012).**

Type 1 AIP is the pancreatic manifestation of IgG4-related disease (IgG4-RD); consequently, a variety of systemic lesions with IgG4-positive cells infiltrates develop simultaneously or metachronously, in association with elevated level of serum IgG or IgG4 (> 135 mg/dL) and positive serum autoantibodies **(Matsubayashi et al., 2013).**

Type 2 AIP

Type 2 AIP is regarded as a specific pancreatic disease, characterized histologically by idiopathic duct-centric pancreatitis (IDCP) with a granulocyte epithelial lesion (GEL). These changes may lead to the destruction and obliteration of the duct lumen, seen in the medium to small-sized ducts and also in the acini **(Kamisawa et al., 2011).**

Patients with type 2 AIP have no serological markers of autoimmunity. Therefore, the classification of type 2 AIP as a clinical entity of AIP is still debated. Nevertheless, the deposition of C3c and IgG in the basement membrane of the pancreatic ducts and acini suggests an immune complex-mediated destruction of ducts and acini in type 2 as well as type 1 AIP **(Detlefsen et al., 2010).**

**Table (2):** Characteristics of clinicopathological findings in type 1 and type 2 autoimmune pancreatitis **(Zhang et al., 2011).**

| | Type 1 AIP | Type 2 AIP |
|---|---|---|
| **Geographical distributuion** | Asia > United States, Europe | Europe > United States > Asia |
| **Age at presentation** | 60-70 s | 40-50 s |
| **Gender** | Male > Female | Male = Female |
| **Symptoms** | Jaundice, abdominal pain | Jaundice, abdominal pain |
| **Serology** | IgG4, IgG, Autoantibodies | Usually negative |
| **Pancreatic images** | Enlarged (focal, diffuse) | Enlarged (focal, diffuse) |
| **Pancreatic histology** | LPSP | IDCP with GEL |
| **Extrapancreatic lesions** | Sclerosing cholangitis, sialoadenitis, retroperitoneal fibrosis, interstitial nephritis, etc. | Inflammatory bowel disease |
| **Steroid response** | Excellent | Excellent |
| **Relapse** | High rate | Rare |

**AIP:** Autoimmune pancreatitis; **LPSP:** Lymphoplasmacytic sclerosing pancreatitis; **IDCP with GEL:** Idiopathic duct-centritic pancreatitis with granulocyte epithelial lesion.

- **Diagnostic criteria of AIP:**

One of the defined sets of diagnostic criteria is HISORt, which summarizes the five cardinal features of AIP through histologic, imaging, and serologic findings; other organ involvement; and response to steroid therapy **(Chari, 2007).** The diagnostic criteria of Japan Pancreas Society in 2018 depends also on the common five previous diagnostic items. (Kawa **et al., 2018)**

Exclusion of pancreatobiliary malignancies is necessary for the diagnosis of AIP, especially in atypical cases. Today, the diagnosis of pancreatic mass lesions by EUS-FNA provides a sensitivity for detecting PC tissue that exceeds 90% (91%-93%), making EUS-FNA the most effective tool for excluding pancreatic malignancies **(Haba et al., 2013).** However, core biopsy using a large-caliber needle may increase the chance of a definitive histological diagnosis of AIP **(Kanno et al., 2012).**

**Table (3):** Imaging features of focal AIP and PC **(Graziani et al., 2014).**

| Investigation | Focal AIP | Pancreatic cancer |
|---|---|---|
| Dual phase CT | Decreased enhancement in pancreatic phase, normal or delayed enhancement in hepatic phase. | Decreased enhancement in pancreatic phase, decreased or minimal increase in enhancement in hepatic phase. |
| **MRI** | -Speckled appearance within hypo-intense lesion.<br>-Low diffusion coefficient on DW-MRI | -Target-like lesion with upstream dilatation of MPD.<br>-High diffusion coefficient on DW-MRI. |
| **FDG-PET CT** | Diffuse FDG uptake<br>Uptake in salivary gland and kidney | Focal FDG uptake. |
| **ERP/pancreatography** | Long segment narrowing of MPD > 3 cm, skip lesions, upstream dilatation of MPD < 5 mm, side branch dilatation from narrowed MPD. | Complete MPD obstruction, short segment narrowing <3 cm, upstream dilatation of MPD > 5 mm. |
| **ERC/cholangiography** | -Lower bile duct stenosis smooth margins, gradual and symmetric narrowing, and fully visible lumen or hourglass appearance.<br>-Intrahepatic biliary stricture. | Short segment stenosis irregular margins, complete obstruction. |

| | | |
|---|---|---|
| **EUS** | -Hyperechoic spots in a hypoechoic mass and the duct-penetrating sign.<br>-Delayed enhancement in CHE-EUS.<br>-Increased thickness of CBD with "sandwich pattern"<br>-Peripancreatic lymphadenopathy | -Hypoechoic mass with inhomogeneous pattern.<br>-Low contrast uptake index on CHE-EUS. |
| **EUS elastography** | Strain ratio <4, hue histogram value <175 | High strain ratio >18, hue histogram value >175. |
| **EUS-FNA, EUS-TCB** | -High stromal cellularity with lymphoplasmacytic infiltrates.<br>-High immunochemical staining with IgG4. | Features of carcinoma. |

MPD: Main pancreatic duct.

FDG-PET CT: Fludeoxyglugose positron emission tomography CT

CHE-EUS: Contrast harmonic echo endoscopic ultrasound.

EUS-FNA: Endoscopic ultrasound guided fine needle aspiration.

EUS-TCB: Endoscopic ultrasound guided trucut biopsy.

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