

Review

Pathognomonic Signs in Pancreatic Cystic Lesions: What Gastroenterologists and Involved Clinicians Need to Know

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Abstract: Pancreatic cystic lesions (PCLs) have been increasingly identified in recent years, encompassing a wide spectrum ranging from benign non-evolutive to malignant invasive lesions. Despite various clinical, laboratory, imaging, endoscopic ultrasound, and cytohistological features that may aid clinicians in the complex differential diagnosis of PCLs, only a few pathognomonic signs distinctive to specific PCLs have been identified. Although rarely encountered, their proper recognition is crucial for the appropriate management of PCLs. The aim of our review is to extensively discuss and illustrate pathognomonic signs in the setting of PCLs.

Keywords: pancreatic cystic lesions; intraductal papillary mucinous neoplasm; mucinous cystic neoplasm; serous cystic neoplasm (SCN); cystic lymphangioma; endoscopic ultrasound

1. Introduction

Pancreatic cystic lesions (PCLs) encompass a broad spectrum of entities, exhibiting a wide variability in biological behavior, ranging from benign to premalignant to malignant lesions [1,2]. They can be classified into epithelial, non-epithelial, neoplastic, and non-neoplastic [1–3]. The epithelial neoplastic group includes mucinous and non-mucinous lesions, which account for approximately 90% of all PCLs [4]. Due to the increased frequency, improved quality, and enhanced accessibility of cross-sectional imaging techniques, PCLs are being increasingly encountered in clinical practice, with an estimated incidence ranging from 3% to 15% and increasing with age [5]. Worth mentioning, PCLs have been reported as incidental findings in 13% to 20% of imaging examinations performed for unrelated reasons [6].

The accurate diagnosis of PCLs is an essential step for appropriate surveillance and management. However, the differential diagnosis of PCLs is complex, often requiring a multidisciplinary approach. To date, no single test has proven accurate enough to diagnose all PCLs [7].

Despite various clinical, laboratory, imaging, endoscopic ultrasound (EUS), and cytohistological features that assist in unraveling the diagnostic puzzle of PCLs, only a few

pathognomonic signs distinctive to particular PCLs have been identified. Given their extremely high diagnostic value, involved clinicians should actively search for these signs and be highly confident in their identification.

Our review aims to discuss and illustrate the pathognomonic signs associated with PCLs.

2. Pathognomonic Signs in PCLs

The following pathognomonic signs will be discussed: central stellate scar, ovarian stroma, chylous cystic fluid with high triglyceride levels, fish mouth papilla, and superficial vascular network pattern (Table 1).

Table 1. Pathognomonic features in pancreatic cystic lesions.

Pathognomonic Sign	PCL	Diagnosis	Notes
Central stellate scar	SCN	Imaging (CT, MRI, EUS)	- 20–30% of cases - May be calcified or non-calcified - Best assessed by CT
Ovarian stroma	MCN	Histology and IHC	- Not detectable on cytology of EUS-FNA-obtained cyst fluid - Typically identified at surgical pathology - Needed for a definitive diagnosis
Chylous cyst fluid with high triglyceride levels	CL	EUS-FNA and cyst fluid analysis	- When not present, a certain diagnosis is difficult and surgery may be needed
Fish mouth papilla	IPMN	Endoscopy	- <30% of cases - More common in main-duct and mixed IPMN - Best assessed by duodenoscopy
Superficial vascular network pattern	SCN	EUS-nCLE	- May not be detected in cases of poor EUS-nCLE technique or epithelial denudation in oligocystic SCA

PCL: pancreatic cystic lesion; SCN: serous cystic neoplasm; CT: computed tomography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound; MCN: mucinous cystic neoplasm; IHC: immunohistochemistry; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; CL: cystic lymphangioma; IPMN: intraductal papillary mucinous neoplasm; EUS-nCLE: endoscopic ultrasound-guided needle-based confocal laser endomicroscopy.

2.1. Central Stellate Scar

The central stellate scar is an imaging finding considered pathognomonic for serous cystic neoplasms (SCNs) [8,9]. It refers to an irregular, star-shaped, dense fibronodular core located at the center of the lesion, with or without calcifications ('sunburst' calcifications), from which thin fibrous septa radiate to the periphery. This scar likely results from the fibrous wall of a centrally located, collapsed cyst. The central stellate scar may be detected through computed tomography, magnetic resonance imaging, and EUS [3].

The most common microcystic variant of SCN is characterized by numerous (typically >6) small internal cysts (<20 mm of diameter) separated by thin fibrous septa, which depict its typical 'honeycomb' or 'sponge-like' appearance [8]. These septa may occasionally centrally coalesce into the so-called stellate scar. Conversely, it is virtually never encountered among the less common variants of SCNs, including the macrocystic (oligocystic), pseudosolid, and mixed serous-neuroendocrine variants [10,11]. Microscopically, the cystic spaces of SCNs are always lined by a single layer of flattened-to-cuboidal epithelial cells, with the central stellate scar being composed of acellular collagenous connective tissue [10,12]. Notably, the central stellate scar has been likened to focal nodular hyperplasia [12].

Although pathognomonic, the central stellate scar is encountered in only approximately 20–30% of cases [13].

An accurate differential diagnosis of the central stellate scar is crucial. Indeed, central stellate scars may resemble a solid portion or the papillary projection of an intraductal papillary mucinous neoplasm (IPMN) [3]. In such cases, evidence of ductal involvement in IPMN and/or the presence of a microcystic component in SCN is crucial for appropriate differentiation [3]. Furthermore, calcifications may be seen in other PCLs, including mucinous cystic neoplasms (MCNs), IPMNs, solid pseudopapillary neoplasms (SPNs), cystic neuroendocrine tumors (NETs), and pseudocysts [14]. The calcifications observed in

SCNs are almost always located within the central stellate scar, as opposed to the peripheral curvilinear or ‘eggshell’ calcifications detected in MCNs, which are typically located within a thickened cyst wall or septum [8,14,15]. Notably, calcifications are encountered in approximately 15% of MCNs and have been reported to be associated with a higher risk of malignancy [16]. Although less frequent, calcifications may also be encountered in IPMNs. Their formation is likely due to the presence of mucin and its tendency to build up calcium salt deposits [16]. Calcifications in IPMNs may be single or multiple, and their location may be mural, septal, or intraductal. Punctate calcification is the most common pattern, followed by coarse and ‘eggshell’ calcifications [16]. Unlike MCNs, their presence in IPMNs has not been correlated with a higher risk of malignancy [16,17]. Furthermore, calcifications are observed in approximately 30% of SPNs, where they are typically peripheral and punctate [16]. Calcifications may also be detected in NETs. They are more common among non-hyperfunctioning and larger NETs due to blood supply outgrowth, which causes cystic changes and dystrophic calcifications. The calcifications are generally centrally located, with a coarse, focal, and irregular pattern [16]. Finally, pseudocysts may very rarely calcify, showing an outer rim of calcification. In this rare instance, other imaging features of chronic pancreatitis are generally present [16]. A case of SCN with the central stellate scar is illustrated in Figure 1.

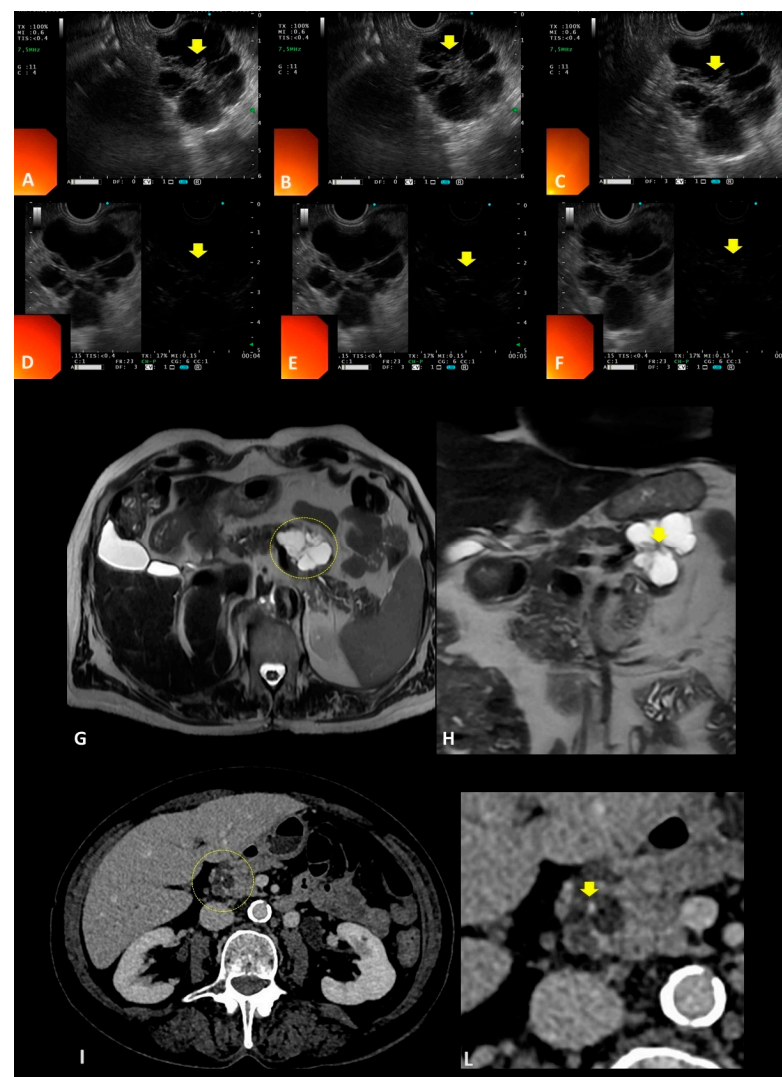


Figure 1. Central stellate scar. (A–C): Endoscopic ultrasound view showing a 35 mm multicystic lesion with lobulated contour of the pancreatic body, with a centrally located non-calcified hyperechoic stellate

scar (arrow), from which thin, delicate septa radiate to the cystic wall. (D–F): Contrast-enhanced endoscopic ultrasound view showing an enhancing central stellate scar (arrow) and internal septa. (G,H): Axial (G) and coronal (H) T2-weighted magnetic resonance imaging showing a high-signal-intensity polylobulated structure in the pancreatic body (dashed circle, G). The structure features fibrous septa radiating from a non-calcified central scar (arrow, H), with no visible communication between the cystic lesion and the main pancreatic duct. (I,L): Axial computed tomography venous phase showing a 30 mm polylobulated cystic lesion (dashed circle, I) in the pancreatic head. The lesion exhibits a calcified central stellate scar (arrow, L).

2.2. Ovarian Stroma

The ovarian stroma is a histological feature considered pathognomonic for MCNs [18]. Histopathologically, the cyst wall and septa of MCNs characteristically contain densely cellular ovarian-like stroma, which regularly stains positively for progesterone receptors and, to a lesser degree, for estrogen receptors [10,11].

The ovarian stroma is an entity-defining feature of MCNs, explaining its almost exclusive occurrence in perimenopausal women [3]. Worth mentioning, the presence of ovarian stroma is currently regarded not only as a pathognomonic sign but also as a requirement for the diagnosis of MCNs [18–21].

Notably, the ovarian-like stroma may not be detected on cyst fluid obtained through EUS-guided fine-needle aspiration (EUS-FNA), but rather only in the surgical specimen [19–21]. However, intriguingly, the identification of ovarian stroma using EUS-guided through-the-needle biopsy forceps has been reported in a patient affected by MCN with denuded epithelium [22].

The ovarian stroma of MCN is illustrated in Figure 2.

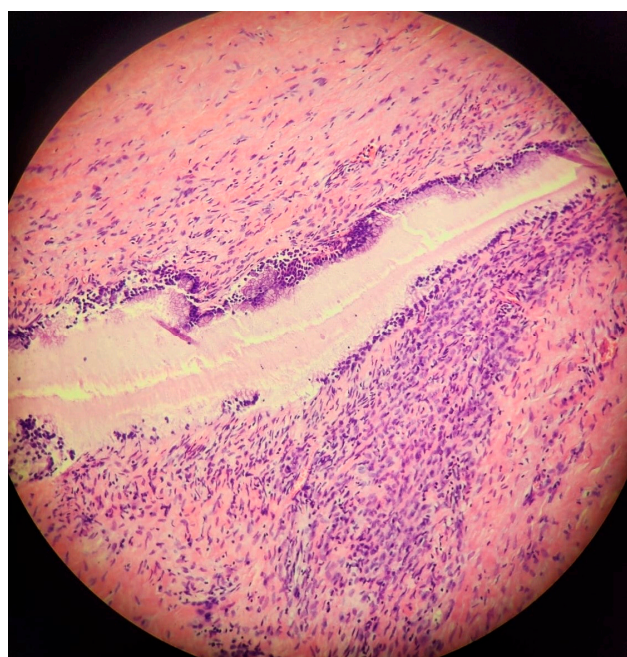


Figure 2. Ovarian-like stroma. Mucinous cystic neoplasm characterized by mucin-producing columnar epithelium with mild dysplasia (upper side) and ovarian-like stroma (lower side) (Hematoxylin-Eosin stain; $\times 200$).

2.3. Chylous Cyst Fluid with High Triglyceride Levels

The presence of chylous cyst fluid with high triglyceride levels is considered pathognomonic for cystic lymphangiomas (CLs) [23]. Pancreatic CLs are extremely rare benign tumors of the lymphatic system, accounting for approximately 0.2% of all PCLs [24]. They are believed to result from lymphatic flow obstruction, leading to lymphangiectasia, which

can be congenital or, less frequently, secondary to inflammation, trauma, radiotherapy, or surgery [25,26].

EUS-FNA of a typical milky cyst fluid with high triglyceride levels greater than 3000 mg/dL on cyst fluid analysis is currently considered sufficient to establish a definitive diagnosis of CL [27–30]. However, it is noteworthy that milky fluid without high triglyceride levels may also be encountered [31]. False-negative results due to technical issues in assessing triglyceride concentration within the intracystic fluid have been reported [31]. In such complex scenarios, intracystic fluid cytology may aid in guiding the correct diagnosis. Nevertheless, surgical referral may still be necessary [27,32].

2.4. Fish Mouth Papilla

The fish mouth papilla, also known as the fish eye papilla, is an endoscopic sign regarded as pathognomonic for IPMNs [7,9]. It refers to a patulous, enlarged orifice of the duodenal papilla, typically associated with active mucus extrusion [33]. IPMNs are neoplasms of mucin-producing cells that arise in the main pancreatic duct and/or its branches. The affected ducts are dilated and filled with neoplastic papillae and mucus to varying degrees. Based on cytoarchitectural features and immunophenotype, IPMNs are classified into gastric, intestinal, pancreatobiliary, and oncocytic histopathological types [34].

Best assessed using a duodenoscope, the fish mouth papilla is observed in fewer than 30% of IPMNs [7], mainly in the main-duct or mixed type [34–36]. Conversely, it is rarely seen in branch duct IPMNs, almost exclusively when located near the papillary orifice [34–36]. Primarily involving the major papilla, this sign may also be rarely observed at the minor papilla, especially in cases of altered anatomy of the main pancreatic duct, such as in pancreas divisum [37].

Notably, the fish mouth papilla has been associated with worrisome features/high-risk stigmata, such as main pancreatic duct dilation ≥ 6 mm and mural nodules [34]. Additionally, it has been significantly correlated with the intestinal type of IPMN, likely due to its higher degree of mucin hypersecretion [34].

The differential diagnosis of a fish mouth papilla mainly includes mucin-hypersecreting bile duct tumors. Although very rarely, these lesions have also been associated with the fish mouth papilla, due to mucin hypersecretion within the bile duct leading to obstruction and subsequent dilation of the papillary orifice [38,39]. However, in such rare instances, the correct diagnosis is usually easily achieved using cross-sectional imaging and EUS.

A case of IPMN with the fish mouth papilla is given in Figure 3.

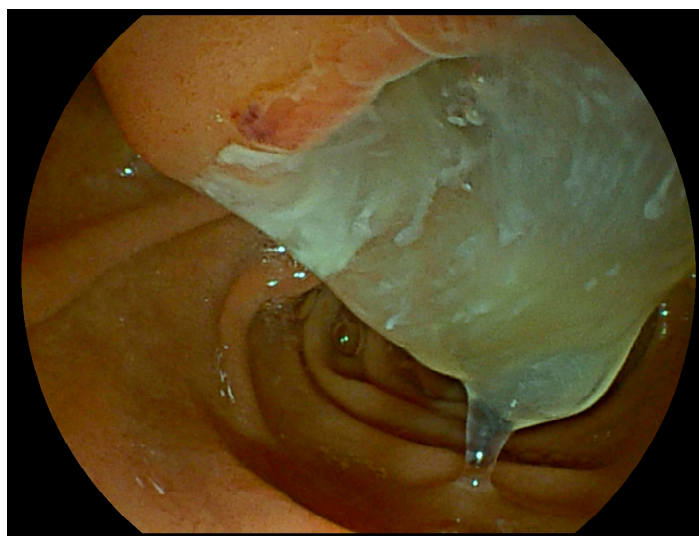


Figure 3. Fish mouth papilla. Endoscopic view showing patulous, enlarged duodenal major papilla orifice, actively extruding a large amount of mucus.

2.5. Superficial Vascular Network Pattern

The superficial vascular network (SVN) pattern, also known as the fern pattern of vascularity, is an EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) feature that may be considered virtually pathognomonic for SCNs [40,41]. EUS-nCLE is a novel imaging technology enabling real-time microscopic evaluation of intracystic epithelium. High-magnification and resolution images are obtained by introducing CLE probes into PCLs through a 19-gauge FNA needle. Moreover, fluorescein is intravenously administered to further enhance blood vessels and other structures of PCLs [41,42].

The SVN pattern refers to a concentrated network of tortuous, parallel vessels of variable width originating from a central vessel [43–45]. Histologically, it corresponds to the characteristic dense subepithelial capillary vascularization of SCNs [43,46,47]. Of note, the SVN pattern may not be detected in cases of poor EUS-nCLE technique or loss of the vascular pattern due to denudation of epithelium in oligocystic SCNs [45,48].

Various epithelial and vascular patterns with high diagnostic accuracy have been reported for the most common types of PCLs [40,41,45]. However, only the SVN pattern has shown 100% specificity across different studies and can be considered a virtually pathognomonic feature [40,41,45]. Nevertheless, EUS-nCLE technology is technically demanding, requiring highly experienced operators, and is not widely available. Finally, large multicenter studies are still needed to confirm the role of EUS-nCLE in PCLs [40,41,45].

3. Conclusions

The differential diagnosis of PCLs may prove challenging, often requiring a multidisciplinary approach to unlock the diagnostic puzzle [7,49]. To date, no single modality has proven accurate enough to diagnose all PCL subtypes [7,49]. While various features seen at cross-sectional imaging, EUS, laboratory tests, and cytohistology may suggest a specific PCL subtype, only a few findings can be considered truly pathognomonic and exclusively indicative of a particular PCL subtype [7]. For example, the presence of a pancreatic duct connection may suggest IPMN, but it may also be observed in other PCL subtypes, such as pseudocysts. Similarly, peripheral ‘eggshell’ calcifications are characteristic of MCNs but may also appear in IPMNs and other rare PCLs [7,14,49–51]. Furthermore, a microcystic component is characteristic but not pathognomonic of SCNs, as it can also be observed in other PCLs, such as CLs [7,28].

Intriguingly, next-generation sequencing of EUS-FNA-obtained cyst fluid has recently shown high sensitivity and specificity for various PCL subtypes. However, this advanced diagnostic tool is not yet widely available due to its high cost, and further studies are needed to validate its promising role in differentiating PCLs [52]. Accurate identification of pathognomonic signs in PCLs is crucial, and involved clinicians should actively search for these signs. Given their impact on PCL management, diagnoses should be made with high confidence, preferably at specialized referral centers. For instance, misinterpreting an ‘eggshell’ calcification as a calcified central stellate scar in an MCN may result in premature discontinuation of surveillance without surgical referral. In conclusion, reliable multidisciplinary collaboration is essential in the diagnostic approach to PCLs and in the proper assessment of their pathognomonic signs to avoid suboptimal classification and risk stratification, which could lead to inappropriate surgical decisions or false reassurances.

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