JOP. J Pancreas (Online) 2007; 8(1 Suppl.):71-76.

CONFERENCE REPORT

Contrast-Enhanced Ultrasonography of the Pancreas

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Introduction

The study of the pancreas is a relatively new application of contrast-enhanced ultrasound (CEUS). CEUS can be used to improve identification, characterization and staging of a pancreatic lesion [1]. The innovative use of CEUS creates the need for a definition for the most frequent features of pancreatic pathology, diffuse and focal, solid and cystic, tumoral and pseudotumoral, in dynamic ultrasound.

Technological Background and Contrast Media

Dynamic ultrasound is different from dynamic CT and MRI in terms of technology and contrast media. CEUS is the only imaging technique which allows a continuous real-time observation of the contrast-enhanced phases, making the identification of fast flow tumoral circulation easier [2]. High temporal resolution of CEUS is one of the most important characteristics of this new imaging modality. The enhancement of a pancreatic lesion can be followed up during the examination [3]. Contrast-specific harmonic software allows maximum contrast resolution during CEUS. Nowadays, the spatial resolution of ultrasound imaging is very high once detailed contrast-enhanced images are obtained. These typical features of CEUS make this method very accurate in perfusional studies (Figure 1).
Moreover microbubbles used for CEUS behave as 'blood pool' contrast agents so that CEUS images of pancreatic tumoral vessels (macrocirculation and microcirculation) are reported to have a very good correlation with the pathologic mean vascular density [4].

Clinical Applications

Pancreatitis

CEUS can improve the ultrasound diagnosis of pancreatitis [5, 6], such as inflammatory pseudotumor. Mass-forming pancreatitis generally occurs in patients with chronic pancreatitis [7]. A differential diagnosis with neoplastic pathology can be challenging, not only due to very similar echographic features [5], but also due to similar symptoms and signs too [8]. Ultrasound findings in mass-forming chronic pancreatitis are very similar to those in ductal adenocarcinoma [5, 7]; in most cases, there is a hypoechoic mass with focal swelling of the gland, generally in the head. Contrast-enhanced examination and biopsy are fundamental for diagnosis. CEUS can help in the differential diagnosis between mass-forming pancreatitis and pancreatic adenocarcinoma [9]. In particular, as adeno-carcinoma remains hypoechoic during all contrastographic phases due to its massive desmoplastic reaction and low mean vascular density, a flogistic mass shows a parenchymographic enhancement in early phases [10]. Application of CEUS in the study of autoimmune pancreatitis has been reported in the literature [11].

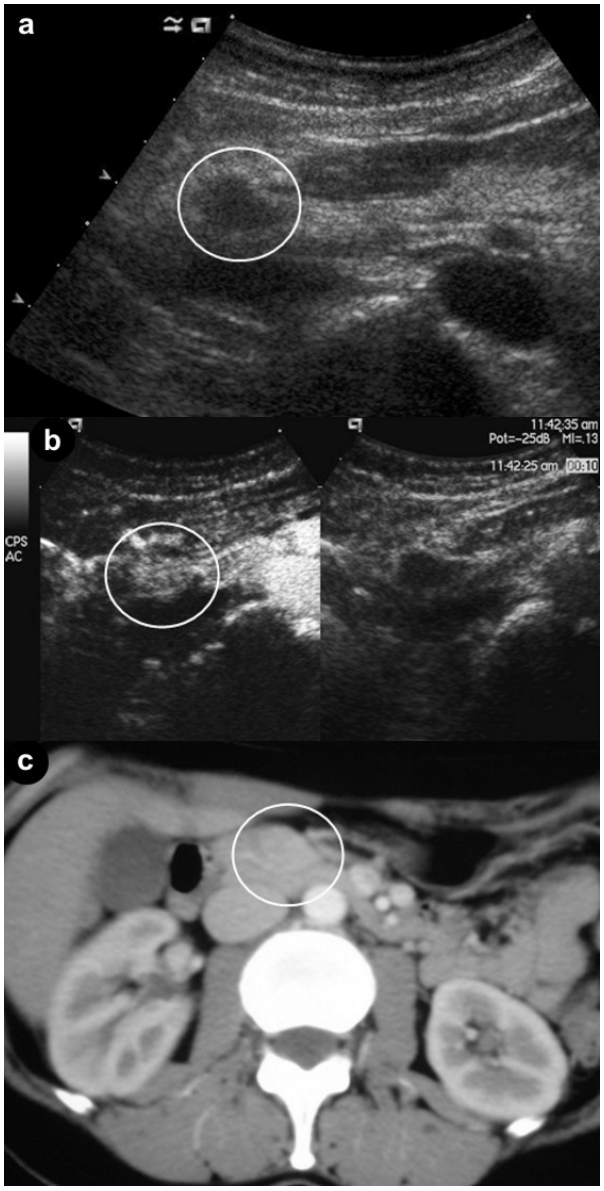

Figure 1. Endocrine tumor. **a.** US: small hypoechoic mass of the uncinate process of the pancreas (circle). **b.** CEUS: the mass is clearly hyperechoic (circle) during the earliest contrast-enhanced phase due to hypervascularization. **c.** CT: the enhancement of the lesion is less evident so that the lesion is quite isodense (circle) as compared to the rest of the pancreatic parenchyma.

Solid Pancreatic Lesions

Pancreatic tumors are divided by histologic type in the WHO classification [12].

Ductal Adenocarcinoma

Ductal adenocarcinoma represents 80-90% of all exocrine pancreatic tumors.

Ductal adenocarcinoma typically appears as a solid mass with infiltrative growth margins. Ultrasound shows a hypoechoic lesion (Figure 2), with ill-defined margins, fading into the surrounding tissue and often bulging from the gland contour, although sometimes, when small, it is completely included in the

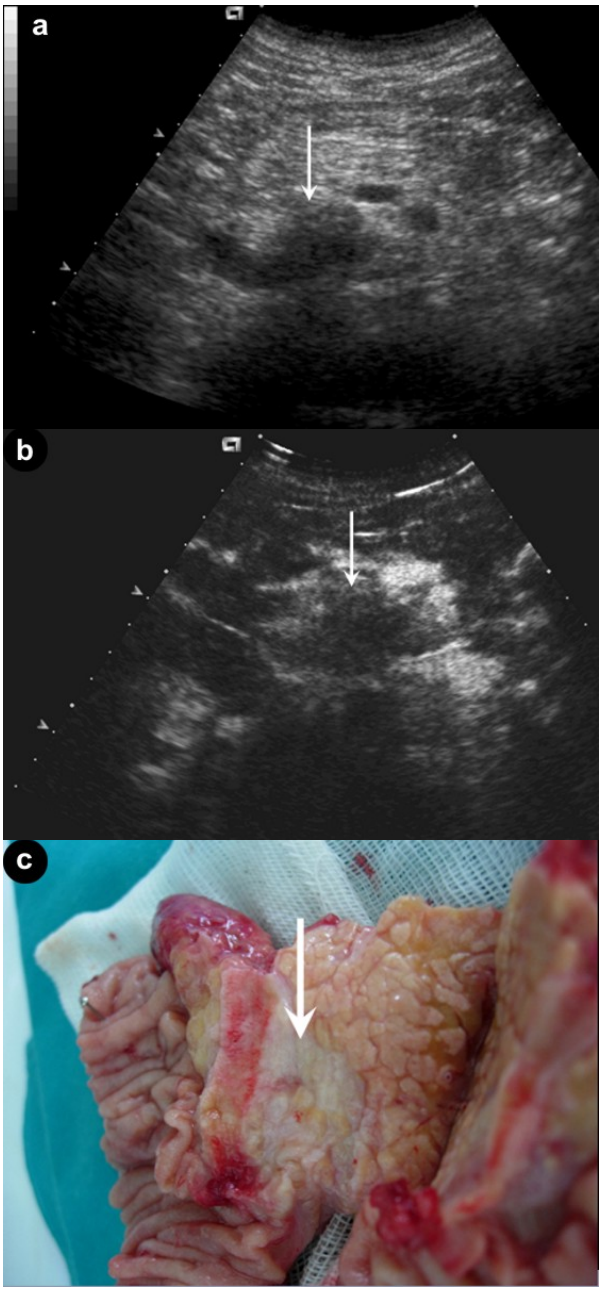

Figure 2. Ductal adenocarcinoma. **a.** US: small hypoechoic mass of the uncinate process of the pancreas (arrow). **b.** CEUS: the mass is clearly hypoechoic (arrow) during the contrast-enhanced phases due to hypovascularization. **c.** Specimen: hard tumoral consistency with marked desmoplasia (arrow) of the resected tumor.

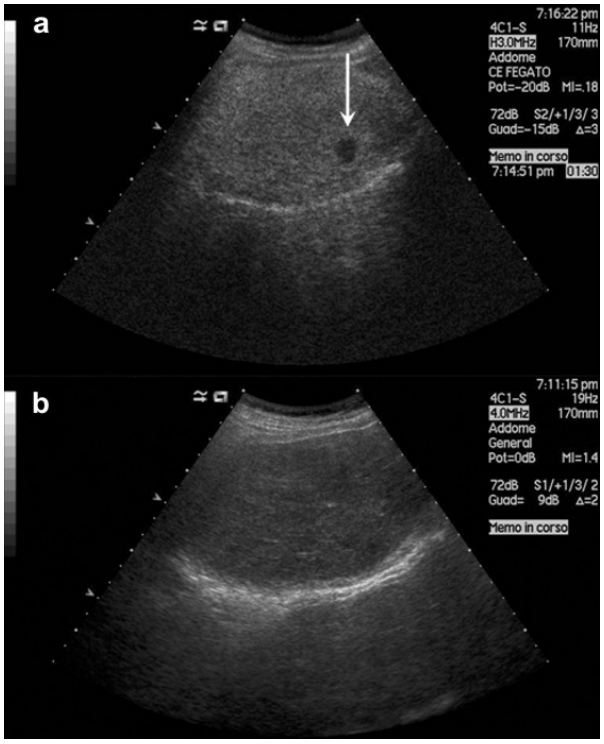

Figure 3. Liver metastasis. **a.** CEUS: a small focal hypoechoic focal lesion of liver dome (arrow) is well-detectable during the sinusoidal contrast-enhanced phase. **b.** US: the lesion was not detected during conventional ultrasound scans of the liver.

pancreatic parenchyma. At CEUS, ductal adenocarcinoma shows poor enhancement during all the contrastographic phases (Figure 2). For the purpose of local staging, the margins and the size of the lesion are more easily observable as is the relationship with arterious and venous peripancreatic vessels (Figure 2). At pathology, adenocarcinoma is characterized by marked desmoplasia [12], causing the hard consistency of the tumor (Figure 2). The mean vascular density is low and often lower than in the normal pancreatic parenchyma.

Locoregional ultrasonographic staging of adenocarcinoma is accurate [13]. Ultra-sonographic contrast medium can improve local staging of pancreatic adenocarcinoma confirming arterious or venous vascular infiltration or involvement. Moreover, CEUS improves hepatic staging, allowing a higher accuracy in the identification and characterization of metastases (Figure 3). After studying a pancreatic lesion during the arterial, pancreatic and venous phases, it is possible to examine the liver for the presence of metastases during the sinusoidal phase of enhancement [14].

Endocrine Tumors

Endocrine tumors can cause specific clinical symptoms owing to hormonal production of the neoplastic cells (functioning endocrine tumors) or aspecific symptoms due to expansive growth and lesion size (non-functioning endocrine tumors). At imaging, endocrine tumors appear hypervascular [15]. An imaging differential diagnosis between non-functioning endocrine tumors and ductal adenocarcinoma is extremely important for prognosis and for determining the approach for therapy [15]. Color-Doppler examination of endocrine tumors shows a pronounced 'spot' pattern [1]; furthermore, hypervascular endocrine tumors can be silent at Doppler owing to the small lesion size or vasculature [1]. CEUS shows different enhancement patterns depending on tumor size and vessels. Large endocrine tumors show a prompt intense enhancement during the early contrastographic phases, except for intralesional necrotic areas where entrapment of microbubbles characterize the late phase [1]. In medium-sized endocrine tumors, a blush-like capillary enhancement can be seen during the early contrastographic phases (Figure 1), reflecting the most characteristic angiographic feature of this neoplasia [16]. Then, these tumors can appear slightly hypoechoic during the late phase [1]. Since characterization of non-functioning endocrine tumors is dependent on their hyper-vascularization [15], an elevated sensibility of imaging techniques is required to identify the macro- and micro-vasculature of the lesion. Finally, as reported, non-functioning endocrine tumors can also be hypovascular [1]. This is directly related to the dense and hyaline stromal component of the lesion. In some endocrine tumors which are hypodense at CT, CEUS recognizes a clear enhancement [1]. CEUS examination can improve the identification [2], the characterization of endocrine tumors [1] and local/hepatic staging [1].

Cystic Pancreatic Lesions

Pseudocysts

Pseudocysts are the most common cystic pancreatic lesions [17] characterized by a fibrous wall without an epithelial lining [17]. At imaging, pseudocysts can be difficult to distinguish from pancreatic cystic tumors [17], especially when containing debris. CEUS improves the sonographic characterization of pseudocysts. Pseudocysts appear completely anechoic during the dynamic phase because of their avascularity, even when they have corpuscolated and non-homogeneous content at basal US. CEUS offers a more confident differential diagnosis between pseudocysts and cystic pancreatic tumors.

Mucinous Cystic Tumor

Mucinous cystadenoma (MCA) is an unusual primitive tumor of the pancreas, although representing the most frequent cystic pancreatic tumor [18]. MCA is considered as a premalignant lesion [19, 20]. It appears as a round cystic mass, multiloculated or less frequently uniloculated, with variable size [21, 22]. The multilocular type is typical, but not pathognomonic [23]. The unilocular type is less common and specific, leading to a differential diagnosis which distinguished it from other pancreatic cystic lesions [24], in particular from pseudocysts [21, 22, 23, 25, 26, 27, 28, 29] and oligocystic serous cystadenoma [18]. MCA can show wall or septal calcifications [29], wall nodules and papillary vegetation [27], whose demonstration is a priority for characterization at imaging. The cystic content can be non-homogeneous for the presence of mucin or intralesional hemorrhage.
At ultrasound, MCA shows cystic areas divided by septa, with a corpuscolar content due to the presence of mucin (Figure 4). Harmonic imaging allows a better evaluation of walls, septa, wall nodules ad papillary vegetation [17]. Moreover, when MCA content is densely corpuscolated, wall nodules can be difficult to identify (Figure 4). CEUS can be of considerable help in identifying wall nodules and septa in MCA and mucinous cystadenocarcinoma (Figure 4). In particular,

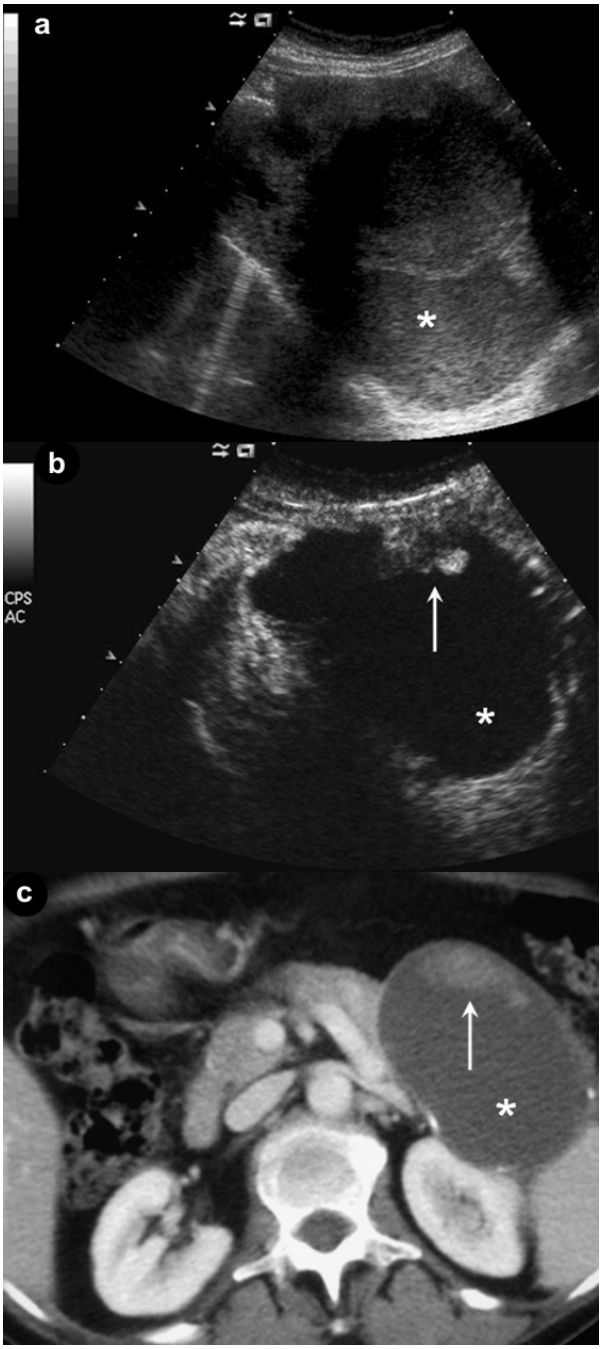

Figure 4. Mucinous cystadenocarcinoma. **a.** US: cystic pancreatic tail mass with non-homogeneous content (asterisk). **b.** CEUS: nodular enhancement (arrow) is clearly visible in the anterior portion of the cystic tumor (asterisk). Note that the non-homogeneous content resulting from mucinous content is no longer visible during the dynamic phases; a better situation for septa and nodules detection. **c.** CT: cystic pancreatic tail mass (asterisk) with a hyperdense nodule on the anterior wall of the lesion.

thanks to the dynamic observation of the contrastographic phases, CEUS allows to detect nodules and septa enhancement. They become hyperechoic because of their vascularization, are more evident in comparison to the avascular lesional content (Figure 4) and are anechoic at dynamic imaging [30]. Moreover, CEUS improves the ultrasonographic differential diagnosis between mucinous cystic tumors and pseudocysts.

Keywords Adenocarcinoma; Contrast Media; Cystadenocarcinoma, Mucinous; Cystadenoma, Serous; Diagnosis, Differential; Microbubbles; Pancreas; Pancreatic Pseudocyst; Pancreatitis

Abbreviations MCA: mucinous cystadenoma

Conflict of interest The authors have no potential conflicts of interest

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Document URL: http://www.joplink.net/prev/200701/25.html

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