

## The Various Imaging Aspects of Chronic Pancreatitis

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### 1. The Early Phase of Relapsing Pancreatitis

The first aspect of chronic pancreatitis (CP) is the early phase of relapsing pancreatitis (RP) in which episodes of mild acute pancreatitis (MAP) or severe acute pancreatitis (SAP) occur repeatedly over a period of time [1, 2]. In RP modifications occur mainly at the ductal structures. These can be functional (altered response to secretin administration, late discharge of pancreatic juices into the duodenum) and/or morphological (ectasia of the branch ducts, irregularity of the main duct walls), or so minute that imaging cannot depict them.

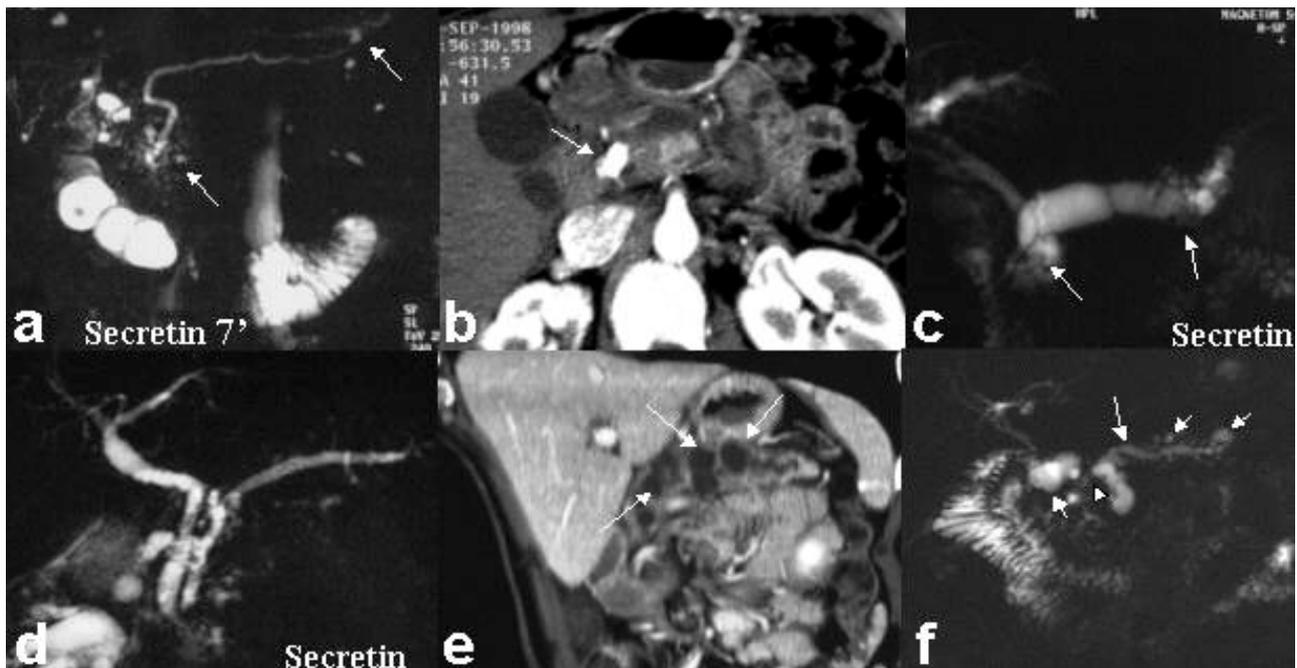
The morphology, the dimensions and the structure of the pancreatic gland are normal at ultrasonography (US), computed tomography (CT: Figure 1a) and magnetic resonance (MR).

The ductal structures may be normal (Figure 1a) or dilated in relation to the size of the obstruction. In this phase, the diagnostic contribution of imaging lies in identifying a series of pathologies which are all rather different, but are all responsible for impairing the flow of pancreatic and/or biliary juice into the duodenum: at the biliary tract, imaging can demonstrate microlithiasis of the common bile duct and/or papilla [3, 4, 5, 6], postinflammatory papillary stenosis, dysfunction of the sphincter of Oddi [4, 6], ampullary tumors and congenital anomalies [7, 8, 9]; at the pancreatic ductal system

imaging can reveal tumors, congenital anomalies [4, 10, 11, 12, 13, 14] and SAP effects [15] and, finally, at the duodenum, imaging can identify tumors, congenital anomalies and duodenal dystrophy.



**Figure 1. Relapsing pancreatitis (a. b. c. d.).** Contrast enhanced SSCT in the pancreatic phase (a. b.); MRCP before (c.) and after (d.) secretin administration. **Papillary adenocarcinoma (a. b.).** The pancreas shows normal morphology and size, preserved parenchymography, notable dilation of the intrahepatic biliary tracts (a.) and choledochus (arrow); small mass (arrow) in the papillary region (b.), jutting into the lumen of the lower knee of the duodenum with a solid density and slightly vascularized in the pancreatic phase after contrast medium. **Lithiasis of the common bile duct (c.).** Endoluminal filling defect (arrows) in the pre-papillary common bile duct (microlithiasis). **Congenital lesions: pancreas divisum (d.).** MRCP examination demonstrates the intersection of the common bile duct (arrowhead) and the dorsal pancreatic duct (arrow), thus confirming the presence of pancreas divisum.



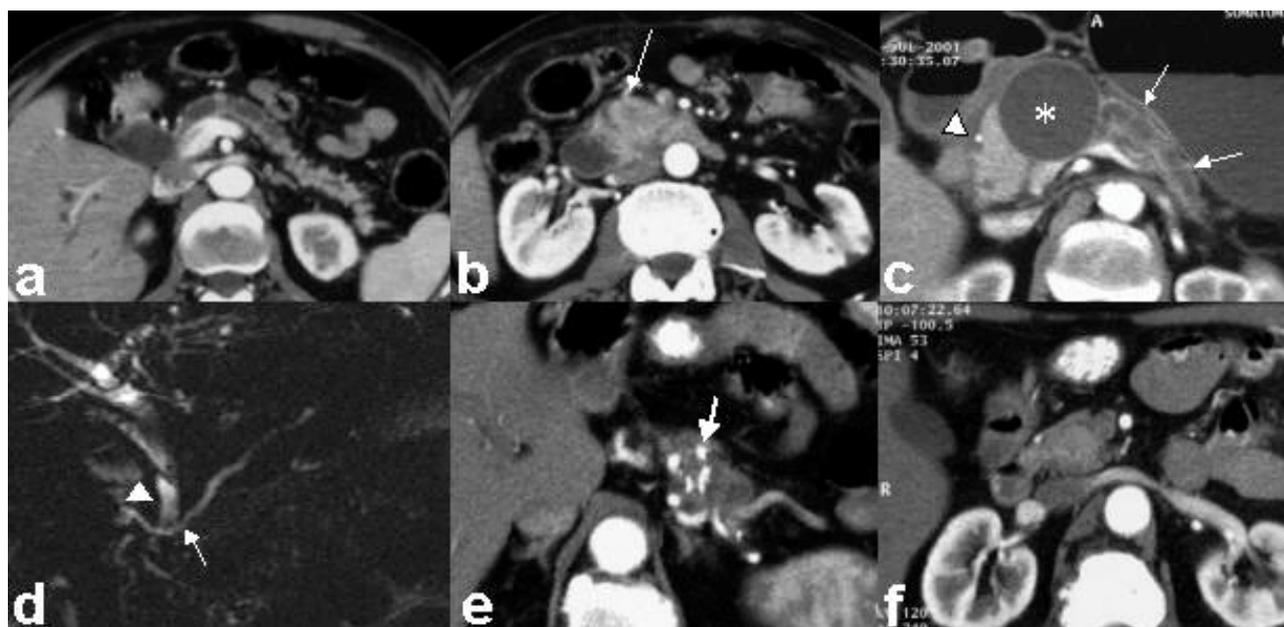
**Figure 2.** Chronic pancreatitis in the early phase (a). MRCP after secretin administration. Mild duct dilation with normal gentle taper, associated with some mild mural irregularity and side branches ectasia (arrows). Duodenal filling is normal. Chronic pancreatitis in the advanced phase: obstructive chronic pancreatitis (OCP) (b, c, d). At contrast enhanced SSCT examination in the pancreatic phase (b), the pancreas is smaller, there is parenchymal atrophy and uniform dilation of the main duct with endoluminal stones (arrow). At MRCP examination with secretin administration (c, d.) uniform dilation and loss of the normal gentle taper of the main duct with endoluminal (c.) filling defects (stones; arrows), without duodenal filling (d.). Imaging differential diagnosis: OCP vs. IPMT (e, f). At contrast-enhanced coronal MDCT examination in the pancreatic phase (e.), total parenchyma atrophy, irregular and notable main pancreatic duct dilation; side branches are dilated (arrows). MRCP (f.) demonstrates dilated mucin-filled main duct (long arrow), with filling defect (neoplastic papillary vegetation: arrowhead) and ectasia of the branch ducts (short arrows) forming a mass with lobulated contours of the pancreatic head and uncinata process.

CT plays an initial diagnostic role at this point as it is more easily able to identify neoplastic causes (Figures 1a, 1b) of RP. Magnetic resonance cholangiopancreatography (MRCP) after secretin administration is the most accurate and non-invasive imaging technique in identifying biliary and/or papillary microlithiasis (Figure 1c), dysfunction of the sphincter of Oddi, congenital abnormalities such as pancreas divisum (Figure 1d), anular pancreas, duodenal diverticulum, duodenal duplication, early stage choledochal cysts [16, 17]; adequate treatment of such lesions can help to impede any subsequent development into CP.

## 2. Chronic Pancreatitis in the Early Phase

In time, repeated episodes of RP lead to the establishment of irreversible anatomic changes of the parenchyma and the ductal structures. These are initially limited but later cystic ectasia of the branch ducts and subtle irregularities in the wall of the main duct appear.

These subtle ductal changes involved with chronic pancreatitis in the early phase are, however, so minute as not to be identifiable at CT examination [18] but are identifiable at MRCP after secretin administration [19].



**Figure 3.** Chronic pancreatitis in the advanced phase: obstructive chronic pancreatitis (OCP) (a. b. c. d. e. f.). Causes. Slow growing tumors (a. b.). SSCT in the pancreatic enhancement phase. The pancreas is smaller, there is parenchymal atrophy, the main pancreatic duct is dilated along its whole course (a.) due to the prolonged obstructive effect of a mass (b.) in the papillary region (arrow), vascularized, and jutting into the duodenal lumen (non functioning neuroendocrine papillary tumor). Pseudocyst (c.). SSCT in the pancreatic enhancement phase. Parenchymal atrophy and uniform dilation of the main pancreatic duct at the body-tail (arrows) which stops at the side of pseudocyst (asterisk). This is a result of previous severe acute pancreatitis, which has shifted the gastroduodenal artery to the right (arrowhead). Congenital lesions: pancreas divisum (d. e. f.). MRCP examination (d.) demonstrates the intersection of the common bile duct route (arrowhead) and the dorsal pancreatic duct (arrow) thus confirming the presence of pancreas divisum. The dorsal pancreatic duct has uniform dilatation and mural irregularities. At SSCT examination in the pancreatic enhancement phase (e. f.) there are small ductal stones (e. arrow) in the pancreatic body only (dorsal pancreas); the posterior half of the head and the uncinata process (ventral pancreas) are normal (f.).

Secretin administration improves pancreatic duct visualization due to both increased ductal caliber and increased fluid content which improves signal intensity.

Mild ductal dilation with loss of the normal gentle taper and usually associated with some mild mural irregularities and side branch ectasia (Figure 2a) represents early changes in CP [20, 21].

### 3. Chronic Pancreatitis in the Advanced Phase

In chronic pancreatitis in the advanced phase, the parenchymal and ductal anatomical changes are by now irreversible and considerable; CT and MR examinations give a more significant diagnostic contribution as they are able to identify and characterize the disease, morphologically distinguishing between obstructive CP (OCP) and non-

obstructive CP (NOCP). They can also categorize OCP by demonstrating some of the possible causes, identifying some particular types of NOCP and finally, differentiate CP from a neoplastic pancreatic pathology, thus helping the clinician make the correct therapeutic choice [22].

#### 3a. Obstructive Chronic Pancreatitis (OCP)

##### *Imaging Characterization of OCP*

OCP has some typical semeiological imaging features in relation to the morphology and structure of the parenchyma and pancreatic ducts; as a consequence of stenosis or obstruction of the main pancreatic duct (MPD), it is associated with dilation of the pancreatic ducts near the obstruction and atrophy of the acinar cells, with uniform and diffuse fibrosis of the pancreatic parenchyma [22, 23, 24].

### *Parenchyma*

The size of the pancreatic gland, initially normal or mildly reduced, becomes progressively smaller due to increasingly serious parenchymal atrophy which is usually uniform and diffuse [22] upstream of the obstruction (Figures 2a, 3a, 3c). In extreme cases, the parenchyma may almost be no longer recognizable [25].

The regularly drained pancreatic parenchyma proximal to the obstruction [24] appears normal (Figure 3c). This finding is, however, unusual since, in the majority of cases, the obstruction is located at the cephalic tract of the MPD and consequently involves the whole gland [25].

The principal modification in the pancreatic structure before contrast medium administration at imaging examinations is the presence of calcifications (Figures 2b, 3e), which is the commonest and most specific CT manifestation of CP [26].

In reality, the calcifications are located between the ducts as they are the consequence of calcium deposits in the form of endoductal proteic plugs [25, 27]. By completely occupying the lumen of the more peripheral ducts. They may however appear to have an intraparenchymal location at CT examination. Calcifications appear as areas of signal void on both T1- and T2-weighted MR images. On MR before contrast medium, the pancreatic parenchyma may have diminished signal intensity on fat-suppressed unenhanced T1-weighted images.

After contrast medium administration in the pancreatic phase, the parenchyma affected by CP with advanced fibrous substitution shows reduced and late enhancement [28], thus resulting hypodense at CT examination (Figures 2b, 3a, 3c) and hypointense at MR examination on T1-weighted sequence compared to the normal parenchyma.

In the subsequent venous phase, the parenchyma tends to become hyperdense and hyperintense at CT and MR examinations and then, in the late phase, the hyperdensity or hyperintensity [19, 28] of the fibrotic areas

becomes further enhanced. This finding is more evident in the case of focal fibrosis where areas of fibrosis alternate with areas of normal tissue in the gland itself [25].

In the presence of repeated episodes of acute attacks, it is possible to recognize areas of peripancreatic oedema (a liquid layer in the fatty peripancreatic tissue), free fluid into the anterior pararenal space (pararenal peripancreatic fluid), as well as peripancreatic collections and areas of glandular necrosis [22, 29] which are difficult to identify due to their hypodensity at CT or hypointensity at MR in the pancreatic enhancement phase.

### *Ductal Structures*

A typical element of OCP, which is present beginning with the initial phases of the disease, is the notable, uniform and regular dilation of the MPD [20]; the diameter of the MPD can reach 2-3 cm (the diameter is normally less than 5 mm at the head and 3 mm at the body-tail).

At CT examination, MPD dilation is better evaluated in the pancreatic enhancement phase, where it is evident with its diffuse, uniform and regular increase in diameter. It also has a fluid content surrounded by thinner pancreatic tissue and is more or less hypodense, depending on the fibrotic substitution (Figures 2b, 3a, 3c).

MRCP examination after secretin administration shows a slightly enlarged main pancreatic duct; the progressive tapering pattern of the pancreatic duct, which normally proceeds towards the tail of the gland is lost (Figure 2c). In patients with severe OCP, duodenal filling is significantly less (Figure 2d) than that of normal patients [20, 30].

The branch ducts are generally undamaged [20]. At times, especially later, they can dilate due to fibrotic stenosis favored by stones [31] in pluri-lobulated cystic collections, until they become true cystic formations (retention cysts) with a fluid density and a thin peripheral wall.

In OCP forms, there may be stones inside the lumen of the MPD (Figures 2b, 2c), sometimes in the Santorini duct and the minor

ducts, which further aggravate ductal dilatation, secondary to the calcium deposits inside the intraductal proteic plugs [20, 25]. These are recognizable as small and hyperdense at CT examination (Figures 2b, 3e), hyperechogenic at US examination of the ductal filling defects and areas of signal void on both T1- and T2-weighted MR images (Figure 2c). However, in the obstructive form, stones are less frequent as compared to forms secondary to genetic mutations [25, 32].

CT examination easily recognizes stones [33, 34], especially before contrast medium administration and, compared to standard abdomen radiograms, has the advantage of being able to demonstrate the site of the calcifications inside the pancreatic gland, distinguishing them from calcifications of the splenic artery [27]. At CT examination the stones appear as hyperdense formations, small in size with a punctiform (Figure 3e) or rounded morphology (Figure 2b). The larger ones have a “casted” or irregular morphology, are widely distributed or concentrated in groups or clusters.

Their number and size are variable [32, 35] in relation to the stage of the disease; they generally tend to increase with time. Furthermore, they can appear early in the presence of toxic factors (smoking, alcohol, diet) or qualitative/quantitative changes in lithostatine levels [35].

After endoscopic extraction or lithotripsy, reduction in the number and size of the stones causes dilation to decrease upstream and improves the clinical picture.

Finally, inside the MPD, after derivative surgical interventions, (pancreo-jejuno or pancreo-duodenal anastomosis) or endoscopic treatment aimed at favoring pancreatic juice flow into the intestinal lumen, (lithotripsy, stone extraction, positioning of stents), gas bubbles are often found.

#### *Imaging Categorization of OCP*

An important diagnostic contribution of imaging is the identification of the causes of

OCP, which determine the multiple aspects of OCP and conditions the therapeutic choice.

#### *OCP Secondary to Slow-Growing Tumors*

Imaging, particularly CT, easily identifies the pancreatic and papillary tumors characterized by slow growth which, following a lengthy obstruction of the pancreatic duct, can frequently cause OCP [36]: adenocarcinoma of the papilla (which was mentioned when dealing with RP) and non-functioning endocrine tumors of the papilla (Figure 3b) and pancreas [25, 37] (which appear at imaging examination as a mass often large, capsulated which usually displays intense enhancement in the pancreatic phase in relation to its rich vascularization [25]). Sometimes there are areas of necrosis and calcifications.

The finding of OCP secondary to the presence of ductal adenocarcinoma and acinar carcinoma of the pancreas is less frequent [37, 38, 39, 40, 41]. Downstream from the MPD dilation and parenchymal atrophy [25] a solid mass is visible, hypodense and hypointense at CT and MR examinations after contrast medium administration because of its scirrhous structure, often infiltrating the ductal structures [25] in the ductal adenocarcinoma, or slightly vascularized and capsulated in acinar carcinoma.

Other tumors responsible for OCP are cystic tumors [37] of the pancreas: serous cystadenoma, which, in its most common microcystic form, appears at CT and MR examinations with a fluid density and “honeycomb” aspect after contrast medium administration [25] with numerous thin septa converging towards a central, often calcified, scar which borders small fluid concamerations [25]; mucinous cystic tumors, which almost exclusively involves females, and, with its preferential location in the body-tail, cause dilation of the main duct and glandular atrophy confined to the caudal portion of the pancreas; even rarer are cystic papillary tumors.

### *OCP Secondary to Severe Acute Pancreatitis (SAP) Outcome*

The phenomenon of scarring of the necrotic parenchymal areas and extraglandular collections of severe acute pancreatitis (SAP) can be due to fibrosis which, in turn, can cause stenosis of the main duct. In time, this is responsible for the onset of OCP.

At CT and MR examinations, the pancreas upstream of the obstruction, which can be located in any portion of the gland, appears with a uniform dilation of the main duct, which can either be greatly or slightly extended depending on the site of the fibrostenotic tract. The branch ducts are undamaged, associated with the notable parenchymal atrophy. The pancreatic portions downstream of the obstruction, on the other hand, appear normal. Pseudocysts, a consequence of SAP, due to mechanical obstruction and scarring, can also be responsible for significant ductal stenosis which can persist at the site of the pseudocyst even after the latter's regression, due to spontaneous re-absorption or surgical drainage.

US, CT (Figure 3c) and MR examinations, therefore, demonstrate a large or a small pseudocyst with a fluid density in the glandular parenchyma, the wall of which is often thickened due to organizational phenomena associated with dilation of the main duct and parenchymal atrophy in the upstream pancreatic portions.

### *OCP Secondary to Congenital Lesions*

Congenital lesions of the biliary tracts and duodenum which sustain RP, can in time lead to OCP, if not identified and corrected. Pancreas divisum is of particular importance. At MRCP examination, the diagnosis of pancreas divisum can be suggested by the identification of two separate ducts entering the duodenum. A coronal MRCP image can show a dorsal pancreatic duct which empties into the duodenum at the minor papilla and which does not connect with the common bile

duct entering the major papilla (Figure 3d), indicating pancreas divisum [42].

CT examination is able to reliably suggest the diagnosis of pancreas divisum in the rather advanced phase of OCP by recognizing signs of CP in one single portion of the pancreatic gland.

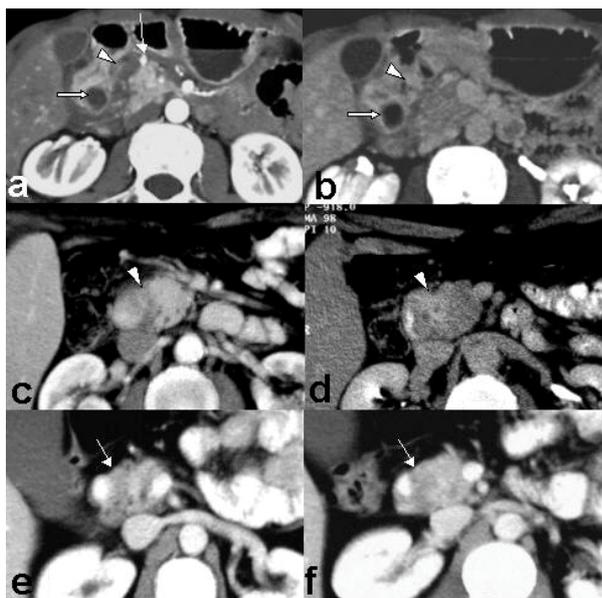
It is common to recognize inflammatory involvement exclusively at the dorsal area of the pancreatic parenchyma with atrophy, dilatation of only the dorsal duct up to its outlet into the minor papilla, and ductal stones (Figure 3e). The ventral area, corresponding to the posterior half of the head and the uncinate process (Figure 3f) is, on the contrary, perfectly normal [32].

At the minor papilla, it is sometimes possible to observe cystic dilation of the Santorini duct with a dense fluid, jutting into the duodenal lumen (Santorinicele). According to some Authors, this is the result of an obstruction associated with an acquired or congenital weakness of the distal wall of the duct [43] caused by functional stenosis of the minor papilla.

Less common is pancreas divisum associated with CP, which inversely involves the ventral segment while the dorsal portion is undamaged. In this case, CT examination may highlight [44, 45] a focal area of the pancreatic head which, in contrast to the rest of the surrounding parenchyma, remains hypodense after contrast medium administration due to often diffuse fibrosis and small calcifications. If the latter are absent, the lesion is rather similar to ductal adenocarcinoma [44], typically hypovascularized after contrast medium administration but, unlike focal ventral CP, is associated with biliary dilation [45].

### *OCP Secondary to Duodenal Dystrophy*

Duodenal dystrophy (DD) is a primitive pathology of the duodenal wall, probably originating from ectopic pancreatic tissue [46, 47]. It appears as a fibrous thickening of the duodenal wall, often associated with chronic inflammation of the intraduodenal pancreatic



**Figure 4.** Chronic pancreatitis in the advanced phase: obstructive chronic pancreatitis (OCP). Causes: duodenal dystrophy and imaging differential diagnosis with ductal adenocarcinoma of the pancreas (a. b. c. d. e. f.). Cystic duodenal dystrophy (CDD) (a. b.). MSCT in contrast pancreatic and late enhancement phases. Thickening of the wall of the second duodenal portion, hypodense in the pancreatic enhancement (a. arrowhead) phase and hyperdense in late enhancement phase (b. arrowhead) due to fibrosis. Within the thickened wall a small formation with rounded morphology and fluid density (thick arrow). Anterior and left-sided dislocation of the gastro-duodenal artery (a. arrow) is present. Solid duodenal dystrophy (SDD) (c. d.). SSCT post-enhancement phases. Thin sleeve of solid tissue (c. arrowhead), hypodense in pancreatic enhancement phases, located between the pancreatic head and the lumen of the second duodenal portion (parietal fibrosis); late and progressive enhancement of the parietal duodenal fibrosis, which, in late (d. arrowhead) enhancement phases, becomes more hyperdense. Ductal adenocarcinoma (e. f.). SSCT post-enhancement phases. A rind of solid tissue between the pancreatic head and the lumen of the second duodenal portion, enhanced by oral contrast medium administration; this lesion is hypodense in the pancreatic enhancement phase (e. arrow) and in the venous phase (f. arrow).

tissue and with cystic lesions located at the sub-mucous or muscular layers [46, 48]. The progression of ectopic pancreatic tissue inflammation, associated with the progressive increase in cystic formations within it, could lead to compression of the MPD and therefore to OCP of the orthotopic pancreas [48].

The only radical therapeutic option to stop this process is surgical resection (duodenal-cephalopancreasectomy). For this reason, the correct imaging diagnosis of DD is important [32, 38, 48, 49], in both its cystic (CDD) or solid (SDD) variants.

The cystic variant (CDD) is identifiable with US, CT (Figures 4a, 4b) and MR examinations as cystic formations can be seen imbedded in the thickened duodenum wall [32] due to the presence of fibrosis [49].

A specific sign of duodenal wall dystrophy [49] is fibrous parietal thickening which appears at CT and MR examinations in the coronal plane [49] as a layer of solid tissue lying between the duodenal lumen and the head of the pancreas. It is isodense at CT and isointense at MR T1-weighted sequence examinations as compared to the gland before contrast medium administration and clearly hypodense at CT examination (Figure 4a) and hypointense at MR T1-weighted sequences as compared to the surrounding parenchyma in the pancreatic enhancement phase [49]. This finding is clearer when the pancreatic parenchyma is undamaged, but less evident if the parenchyma has been substituted by fibrosis in the presence of CP.

Thickening of the duodenal wall tends to have a slow and late enhancement in the venous phase and even more so in the late phase (Figure 4b), due to its fibrous nature [47, 49, 50]. Cystic formations can be seen in the parietal fibrosis [47, 48, 49], located in the space between the pancreatic head and the first, more commonly the second (Figures 4a, 4b) or the third portion of the duodenum, usually on the mesenteric side and more rarely on the anti-mesenteric side. Generally, the cystic lesions are multiple from 3 to more than 10 in number, measuring 3 to 5 mm in diameter [50]. They have a fluid density and, unlike pseudocysts (Figure 3c), their morphology is elongated or plurilobular [40, 49]. They imprint onto the duodenal lumen, which is usually reduced in size (Figures 4a, 4b). There may also be gastric dilation [32, 47, 48, 49, 51]. Finally, since they originate in

the duodenum, the cysts may shift [49] the gastroduodenal artery forwards and to the left (Figure 4a), exactly the opposite of what happens if the pathology originates from the head of the pancreas. In this case, the vessel is shifted to the right (Figure 3c).

In the solid variant (SSD) because the cysts of this variant are smaller than the spatial resolution of US, CT and MR examinations [49], what usually leads to the identification of this pathology is the fibrous thickening of the duodenal wall which is often difficult to distinguish from the pancreatic head and can be mistakenly interpreted as a solid lesion with a pancreatic origin [32, 49].

Before contrast medium administration at CT and MR examinations, only a generic increase in the size of the cephalopancreatic region is identifiable, often associated with gastrectasia and a reduction in the duodenal lumen, which appears irregular. After contrast medium administration, the fibrous thickening of the duodenal wall is distinguishable from the head of the pancreas being clearly hypodense at CT examination (Figure 4c) and hypointense at MR T1-weighted sequence as compared to the pancreatic parenchyma. Having a reduced and late enhancement, it tends to become hyperdense at CT examination (Figure 4d) and hyperintense at MR examination as compared to the pancreatic parenchyma in the venous and late phases.

When distinguishable, the gastroduodenal artery shifts forward and to the left, and can be a further useful indication of a correct diagnosis.

Nevertheless, the cystic and solid dystrophy variants are not always separate entities but different development stages of one single pathological process. Identification by imaging of one or the other variant can alternate in the same patient within a short period of time as the cysts, present but very small, can either increase in size until they become recognizable or, on the other hand, can become even smaller [32], again within a short period of time.

Both forms can demonstrate dilatation and dislocation [49] to the left of the common bile duct which, in the groove tract, becomes gradually narrower.

#### *OCP Secondary to Chronic Inflammatory Stenosis of the Papilla*

Chronic inflammation of the papilla, in the majority of cases following repeated micro-traumas due to the passage of stones and/or biliary sand, can, in time, lead to scarring and stenosis of the sphincter of Oddi and, subsequently, the onset of OCP.

Diagnosis of this form of OCP is mainly entrusted to clinical and functional investigations. CT and MRCP contributions are limited to diagnostic confirmation of this pathology, as they are able to exclude other causes of the ductal obstruction.

#### *3b. Non Obstructive Chronic Pancreatitis (NOCP)*

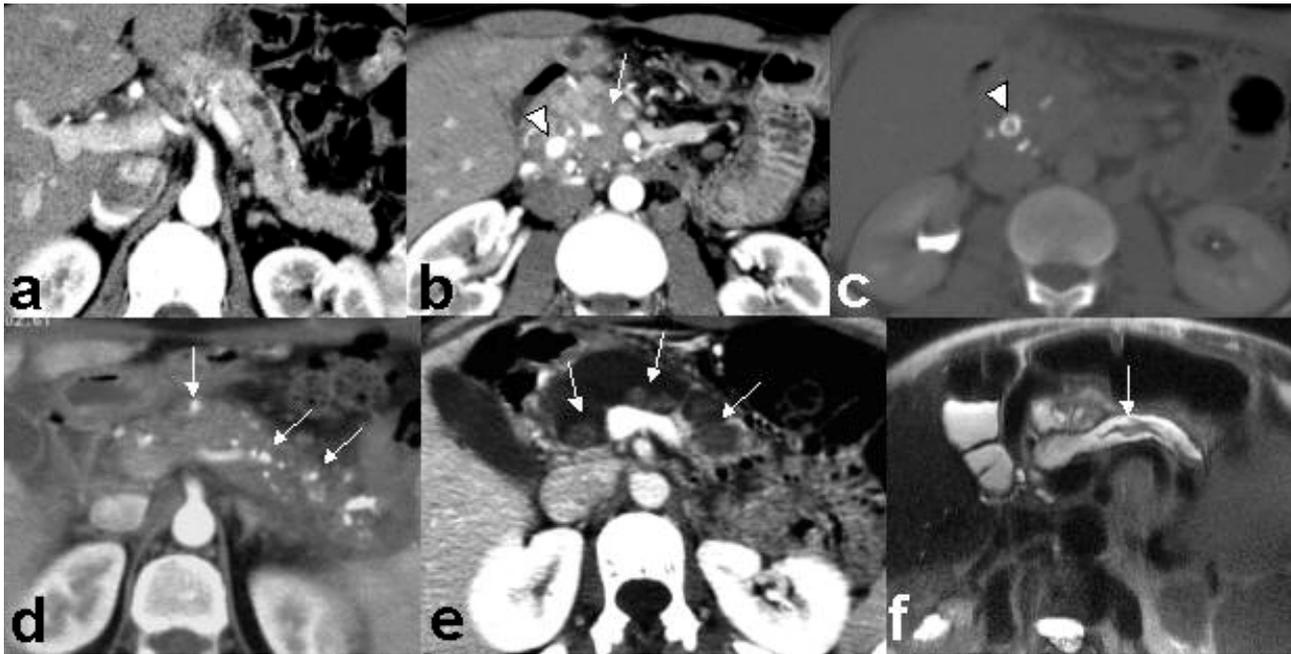
Imaging examinations also give a diagnostic contribution in identifying some aspects of non-obstructive CP, thus providing useful confirmation of the clinical-laboratory suspicion of this disease.

We are not speaking about autoimmune pancreatitis but only about CP secondary to a toxic agent (alcohol) and to genetic mutations.

#### *Imaging Identification: NOCP Secondary to Toxic Agent (Alcohol)*

CP associated with alcohol is often calcific (20-40% of cases) and usually develops after 5-10 years of abdominal pain attacks.

The glandular parenchyma can demonstrate a focal or a diffuse increase in size and an altered parenchymography on CT and MR examinations due to late enhancement after contrast medium administration in relation to the presence of unevenly distributed fibrotic areas. In the advanced phase, there is a fibrotic retraction of the parenchyma until atrophy occurs. The collateral ducts show ectasia which can sometimes become retention cysts. The MPD shows stenotic tracts alternating with the more dilated parts



**Figure 5.** Chronic pancreatitis in the advanced phase: non obstructive chronic pancreatitis (NOCP) associated genetic mutations; imaging differential diagnosis with IPMT of the pancreas (a. b. c. d. e. f.). NOCP associated genetic mutation (SPINK 1) (a. b. c.). SSCT examination in the pancreatic enhancement phase. Twenty years after the first clinical chronic pancreatitis symptoms, CT examination demonstrates dilation of the main duct of the body-tail and normal glandular parenchyma (a.); an hypodense area after contrast medium in the pancreatic phase with respect to the normal parenchyma (fibrosis) is present in the medial side of the head (b. arrow); a ductal stone (b. c. arrowhead) is present in the cephalic level with a central hypodense nucleus (c.) due to the lack of calcification and hyperdense peripheral band (“bull’s eye” aspect). NOCP associated genetic mutation (CFTR) (d. e.). SSCT examination in the pancreatic enhancement phase. Twenty-seven years after the first clinical chronic pancreatitis symptoms, the pancreas is of normal size, the glandular parenchyma is hypodense due to fibrosis and multiple small stones are present in the main pancreatic duct (d. arrows). Eight years after the first clinical chronic pancreatitis symptoms, parenchymal atrophy, dilation of the entire main pancreatic duct, multiple non-enhancing solid deposits (e. arrows) are present (amorphous calcifications in the dilated main pancreatic duct). IPMT (f.). T2-weighted MR image shows conspicuous dilation of the main pancreatic duct within which there is a filling defect, attributed to a mucin deposit (arrow).

and the so-called “rosary crown” appearance [21, 52]. There are multiple stones of variable size and the morphology is often irregular.

#### *Imaging Identification: NOCP Secondary to Genetic Mutations*

Multiple genetic mutations have been associated with the onset of CP, for the most part associated with the cystic fibrosis (*CFTR*) gene, the serine protease inhibitor Kazal type 1 (*SPINK 1*) gene and the cationic trypsinogen (*PRSS1*) gene [23, 29, 53, 54, 55, 56, 57, 58].

Non-invasive imaging examination (CT and MR) is able to supply a valid diagnostic contribution, identifying some changes in the ductal structures and the parenchyma, typical

of NOCP secondary to genetic mutations and useful in making a correct diagnosis.

In the advanced phase [59], the main duct is dilated (Figures 5a, 5e) along its whole length and is often outlined and irregular [60, 32], with a 1- to 2-cm diameter [61] which is less evident in the early phase [61].

In the lumen of the MPD, stones can be usually recognized [27, 60, 61], hyperdense in both CT pre- and post-enhanced phase examination (Figures 5b, 5c, 5d), and like areas of signal void on both T1- and T2-weighted MR images; they are fewer in the early phase becoming more numerous later on and are widely distributed inside the dilated main duct. They are either round or ovular and are often more than 2-3 cm in diameter.

They can have a typical pattern at CT examination with hyperdense peripheral margins and a hypodense center [60, 61] due to the lack of calcium deposits in the central core, an aspect often described by some authors as a “bull’s-eye” (Figure 5c).

In relation to the calcifications present in other CP forms, in NOCP secondary to genetic mutations, the stones tend to appear earlier, are larger [25, 27] and are typically rounded (Figures 5b, 5c), often aligned within the considerably dilated main duct. Therefore, the ductal stones, numerous and large, particularly the “bull’s-eye” type, are a rather characteristic semeiological element of CP secondary to genetic mutations. For this reason, CT examination offers a more informative contribution than MR, which is less sensitive in identifying calcifications [62, 63, 64, 65].

On the contrary, in NOCP associated with cystic fibrosis gene mutations (*CFTR*), the calcifications are generally smaller (Figure 5d) and tend to appear later on as compared to other forms of NOCP secondary to genetic mutations [57]. In the lumen of the MPD, there are often large [57] hyperdense filling defects (Figure 5e).

Nevertheless, pancreatic main duct dilation, pancreatic size and glandular parenchyma are frequently normal or increased (Figures 5a, 5b, 5c, 5d). On CT and MR post-enhanced phase examinations, the parenchymography is abnormal because of fibrosis (Figures 5b, 5d). In the advanced phase, there is serious glandular atrophy [32, 60] with thin and variable enhancement. Some glandular portions can be unaffected or even appear hypertrophic.

Parenchymal fibrosis often causes stenosis of the intrapancreatic common bile duct [59]. Moreover, in hereditary pancreatitis, the incidence of pseudocysts is higher as compared to other forms of CP [56, 59].

#### **4. Imaging Chronic Pancreatitis Differential Diagnosis**

##### 4a. OCP vs. Pancreatic Tumors

Once OCP has been identified at imaging examination, together with some of its potential causes, these techniques also make a valid contribution in differentiating between this pathology and some pancreatic lesions [36, 66].

##### *OCP vs. Intraductal Papillary Mucinous Tumors (IPMT) of the Pancreas*

IPMTs are rare lesions [37, 67] and, although less common and potentially malignant, they have a better prognosis than ductal adenocarcinoma [42, 67]. Because they manifest at imaging in a manner similar to OCP [32, 37, 67, 68], it is important to identify them correctly [37] in order to decide on the appropriate treatment.

Until a few years ago, the only possibility of distinguishing the two pathologies was endoscopic retrograde cholangio-pancreatography (ERCP) which could recognize the secretion of mucin from the papillary pore and the presence of filling defects in the dilated ducts [32] due to solid neoplastic tokens jutting into the lumen or to mucin deposits [42].

Nowadays, with the use of thin layer single-detector CT (SDCT) and even more so using multi-detector CT (MDCT: Figure 2e), thanks to the coronal and curved reconstructions and with MRI and MRCP [68] after secretin administration (Figures 2e, 2f), it is not only possible to identify diffuse dilatation of the MPD, often associated with atrophy of the glandular parenchyma [32, 42, 66, 69, 70], but also some specific signs of IPMT: the presence of hyperdense ductal filling defects due to tiny papillary vegetations on the ductal wall and/or mucin filling defects inside the

ductal lumen; a dilated papilla bulging into the duodenal lumen and cystic ectasia of the branch ducts, more often in the uncinate process (Figures 2e, 2f), and/or dilation of the common bile duct [32, 71].

These CT signs, together with abnormal dilatation of the pancreatic duct and unexplainable parenchymal atrophy that can cause an obstruction, arouse the suspicion of an intraductal tumor [31].

#### *OCP Secondary to Solid Duodenal Dystrophy (SDD) vs. Ductal Adenocarcinoma of the Head of the Pancreas*

Distinguishing between the two entities is not easy as, from the clinical point of view, both diseases have many common features [32] and aspiration biopsy is not always satisfactory [38, 39, 72, 73, 74]. For these reasons, some patients with SDD undergo surgical resection for suspected carcinoma of the head of the pancreas [38, 50].

The contribution of imaging is therefore important. With CT and MR examinations, the particular features of SDD can be better evaluated in the pancreatic enhancement phase [49]. The SDD appears as a fibrous thickening of the duodenal wall better identifiable on the MR coronal plane [49, 32], and has an elongated morphology, which is located externally to the pancreatic head between the latter and the duodenal lumen. The lesion, unlike ductal adenocarcinoma (Figures 4e, 4f), has a reduced and late staining in the enhancement phase being hypodense at CT examination (Figure 4c) and hypointense at MR T1-weighted sequence in the pancreatic phase, less so in the venous phase, while it tends towards hyperdensity at CT examination (Figure 4d) and hyperintensity at MR examination in the late phase [19, 21].

An important sign is the gastroduodenal artery and the dislocation of the common bile duct [32] forward and to the left, which is typical in dystrophy and which further sways the diagnosis towards a lesion of duodenal origin

rather than pancreatic.

It is not necessarily associated with biliary obstruction. When present, however, stenosis of the common bile duct is usually long with regular margins and can regress in time unlike a sudden and progressively serious obstruction which is typical of ductal adenocarcinoma [38, 50, 75].

Endoscopic ultrasound (EU) can distinguish adenocarcinoma from SDD better than CT and MR examinations showing intramural infiltration of the duodenal wall limited to the submucosa and muscularis propria of the second portion of the duodenum with multiple microcysts within the thickened mucosa and submucosa [71].

#### *4b. NOCP vs. Pancreatic Tumors*

##### *NOCP Secondary to Genetic Mutations vs. IPMT*

At CT (Figure 5e) and MR examination, NOCP secondary to genetic mutations associated with the fibrocystic gene mutation (*CFTR*) in the pancreatic phase can appear very similar to an IPMT (Figure 5f). In fact, there is parenchymal atrophy and notable dilation of the main duct in both diseases. In NOCP secondary to the *CFTR* mutation, late-appearing ductal stones are found which are smaller than those found in other types of NOCP from genetic mutations. However, in the lumen of the MPD, large, hyperdense filling defects are often present (Figure 5e), due to proteinic aggregates which are formed because of the high level viscosity of the pancreatic juice. This is typical of cystic fibrosis [57, 71] which appears at CT and RM examinations similarly to the mucin deposits and/or neoplastic papillary vegetation common to IPMTs (Figure 5f).

For this reason, in young patients with a long history of acute pancreatitis attacks and a suspected IPMT at imaging, it is a good idea to carry out a study of the fibrocystic gene mutations before deciding on any surgical resection [57].

#### 4c. Imaging Identification of Ductal Adenocarcinoma in CP

CP is considered as one of the risk factors for the onset of pancreatic ductal adenocarcinoma [2, 37, 76, 77].

CT examination is limited in identifying a ductal adenocarcinoma which begins during CP because of the reduced difference in density between the cancerous lesion, which is typically hypovascularized, and the pancreatic parenchyma, which is also hypovascularized due to the fibrosis. Furthermore, the main duct, obstructed upstream by the lesion, already appears dilated due to the pre-existing chronic inflammatory processes. The frequent presence of endoluminal stones can hide the parenchymal structures.

The hypodensity of the lesion in the pancreatic enhancement phase is, however, always more noticeable as compared to the glandular parenchyma in CP and persists throughout all the phases of the CT examination.

Moreover, the onset of an adenocarcinoma in CP can sometimes be responsible for the displacement of ductal calcifications with respect to previous CT examinations. This indicates the presence of an expansive lesion [22].

The appearance of the pancreatic duct on MRCP may hold some promise in helping to identify carcinoma in CP.

Studies have found that if a non-dilated main pancreatic duct courses through the pancreatic mass, then it is most likely related to focal pancreatitis. On MRCP a normal pancreatic duct or smoothly stenotic duct was seen in 85% of patients with CP and in only 4% of patients with carcinoma (“duct-penetrating sign” at MRCP) [78].

Contrast-enhanced transabdominal ultrasonography (CETUS) is a new technique which has made it possible to depict the fine vessels surrounding the tumor and extending from the periphery to the center of the tumor in real time, facilitating the differential diagnosis of pancreatic tumors. Another advantage of

CETUS is that it improves the depiction of small lesions as compared to fundamental B-mode US [79, 80]. Positron emission tomography (PET) with 2-fluoro-2-deoxy-D-glucose (FDG) was recently introduced into clinical oncology because of its ability to demonstrate metabolic changes associated with various disease processes. Some studies investigated the possibility of identifying pancreatic cancer in CP with FDG-PET [81, 82].

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**Keywords** Cholangiopancreatography, Endoscopic Retrograde; Cholangiopancreatography, Magnetic Resonance; Diagnosis, Differential; Magnetic Resonance Imaging; Pancreatitis; Pancreatitis, Alcoholic; Tomography, Spiral Computed; Ultrasonography

**Abbreviations** CDD: cystic duodenal dystrophy; CETUS: contrast-enhanced transabdominal ultrasonography; CP: chronic pancreatitis; DD: duodenal dystrophy; FDG: 2-fluoro-2-deoxy-D-glucose; IPMT: intra-ductal papillary mucinous tumors; MAP: mild acute pancreatitis; MDCT: multi-detector computed tomography; MPD: main pancreatic duct; ; MSCT: multislice computed tomography; NOCP: non obstructive chronic pancreatitis; OCP obstructive chronic pancreatitis; RP: relapsing pancreatitis; SAP: severe acute pancreatitis; SDCT: single-detector computed tomography; SDD: solid duodenal dystrophy; SSCT: singleslice computed tomography

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