Multidetector row computed tomography pattern in differential diagnosis of diffuse autoimmune pancreatitis and non necrotizing acute pancreatitis at clinical onset

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Purpose

The aim was to retrospectively evaluate the utility of Multidetector Row Computed Tomography (MDCT), in differentiating Diffuse Autoimmune Pancreatitis (DAIP) from Non Necrotizing Acute Pancreatitis (NNAP) at clinical onset.
Methods and Materials

Patient population

This study was approved by our investigation review board.

All consecutive patients diagnosed with DAIP or NNAP within our institution from May 2006 to May 2009 were retrospectively included.

Inclusion criteria were: first episode of DAIP or NNAP diagnosis and abdominal Multiple Detector Row Computed Tomography (MDCT) examination after at least 48-72 hours of the clinical presentation.

DAIP and NNAP diagnosis was made on the basis of clinical data (pancreatic pain, with or without associated jaundice, and fever), laboratory tests (at least three-fold increase above the upper normal limit for serum amylase and/or lipase, serum levels of non-organ specific autoantibodies, increased serum levels of immunoglobulin G4), histopathological specimens and imaging follow-up.

DAIP diagnosis was confirmed by histological specimens with percutaneous biopsy in 4/14 patients in order to exclude pancreatic lymphoma.

The histopathological criteria used to diagnose DAIP were as follows: lymphoplasmacytic infiltration around small pancreatic ducts, swirling fibrosis centered around ducts and veins, and obliterative phlebitis. In the remaining 10/14 patients with suspicion of DAIP, diagnosis was confirmed by normal pancreatic findings at CT follow-up after 2-3 weeks of high-dose corticosteroid treatment.

Seven DAIP Patients had associated autoimmune diseases: 2 Sjogren Syndrome, 2 Ulcerative Colitis, 2 Crohn Disease, 1 retroperitoneal fibrosis and 1 autoimmune pielonephritis.

NNAP diagnosis was confirmed by CT follow-up assessing normal pancreatic and abdominal features after seven days from the onset.

Exclusion criteria were: focal AIP, presence of pancreatic calcifications, diagnosis of Severe Necrotic Acute Pancreatitis (SNAP), previous pancreatic surgical/endoscopical procedure.

A search of our institution's radiology, pathology, internal medicine and emergency room records revealed 36 patients affected by one of the two diseases (22 NNAP, 14 DAIP). The mean age of patients was 52.4 years (age range 21-88 years) at clinical presentation.

Imaging
CT examination obtained between May 2006 to December 2006 were performed in 5 patients on a 6-MDCT scanner (Brillance CT; Philips, Best, The Netherlands) with time rotation of 0.75 seconds. All patients received 500 ml of oral contrast agent (water) 20 minutes before the examination. Quadri-phasic (precontrast enhanced, contrast enhanced pancreatic, portal venous and delayed phases) MDCT was performed. Pre-contrast enhanced images were obtained from the top of diaphragm to the bottom level of the uncinate process. Scanning parameters included 120 kVp, 200 mA, with 6 x 1.5 mm collimation. The reconstruction slice thickness during the unenhanced phase was 2 mm, with a 1 mm interval.

Iodinated non-ionic contrast material (Ultravist 370, Schering, Berlin, Germany) was administered intravenously via power injector (Stellant D Dual Syringe, Medrad, Pittsburgh, USA) as a 120 ml bolus (4 ml/sec) follow by 50 ml saline flush (4 ml/sec). Contrast medium administration involved the use of bolus-tracking software, with an aorta trigger region of interest localized by the technologist. This region of interest encompassed the aortic lumen while avoiding the walls. A contrast material bolus was administrated, and 15 seconds after bolus injection began, low-dose monitoring was performed to track contrast enhancement within the aortic lumen. When a predetermined attenuation threshold (100 HU) was reached, regular scanning was automatically triggered.

Contrast enhanced pancreatic phase images, obtained from 1 cm above the celiac axis and throughout the entire pancreas, were acquired 20 seconds after bolus tracking began (6 x 0.75 mm collimation). Contrast enhanced portal venous phase images, obtained from the top of the diaphragm throughout the kidneys or pelvis (6 x 0.75 mm collimation), were obtained 60 seconds after bolus tracking began. The reconstruction thickness during the pancreatic and portal venous phases was 1 mm, with a 0.50 mm interval.

Contrast enhanced delayed phase images, obtained from the top of diaphragm to the bottom level of the uncinate process, were acquired 180 seconds after bolus tracking began (6 x 1.5 mm collimation); the reconstruction thickness was 2 mm, with 1 mm interval.

CT examinations obtained between January 2007 to May 2009 were performed in 31 patients on a 64-MDCT scanner (Brillance CT; Philips, Best, the Netherlands) with time rotation of 0.4 sec. The same quadriphasic MDCT technique was performed. Pre-contrast enhanced scanning parameters included 120 kVp, 200 mA, with a 64 x 1.25 mm collimation. The reconstruction thickness during the unenhanced phase was 2 mm, with a 1 mm interval.

Contrast enhanced pancreatic, venous and delayed phase images were acquired with 64 x 0.625 mm collimation. The reconstruction thickness during the pancreatic, portal venous and delayed phases was 1 mm, with a 0.50 mm interval.
Quadriphasic curved multiplanar reconstruction images were generated on the CT scanner's workstation for both MDCT scanners.

**Image analysis**

Two radiologists, more than 10 years experienced in gastrointestinal radiology, independently analyzed the images. Discrepancies were resolved by final consensus.

Image analysis was performed by viewing digital axial 6 and 64-all phases MDCT images at a workstation. All phases 64-MDCT curved multiplanar reconstruction images were also included in the image analysis.

All axial and curved multiplanar reconstruction images were qualitatively analyzed for the following characteristics: pancreatic diffuse enlargement (presence/absence), swelling of pancreatic parenchyma (presence/absence). The pancreas was considered to be swollen subjectively when lobular gland architecture was not readily identifiable. Also evaluated in qualitative analysis were: main pancreatic duct dilatation (presence/absence, diffuse/focal: head/body-tail), pancreatic density on pre-contrast enhanced phase (as compared with spleen parenchyma density: hypodense/isodense/hyperdense), pancreatic contrast enhancement during the pancreatic phase (as compared with spleen contrast enhancement: hypodense/isodense/hyperdense), during portal venous phase (as compared with parenchyma contrast enhancement in previous phase: hypodense/isodense/hyperdense), and during the delayed phase (as compared with parenchyma contrast enhancement in portal venous phase: retention/washout). Also analyzed in qualitative analysis were: pancreatic stranding represented by streaking of peripancreatic fat due to edema evidenced as an hypodense halo in all phases of MDCT examination (presence/absence), retroperitoneal fluid film in the left anterior pararenal space due to acute inflammatory changes and edema of retroperitoneal fat (presence/absence), peripheral capsule-like rim enhancement surrounding the pancreas due to chronic inflammatory changes of peripancreatic fat, evidenced as a hypodense halo in pancreatic and venous phases and as a hyperdense halo in delayed phase (presence/absence), and pleural effusion (associated sign of acute abdominal disease).

Quantitative analysis was performed by a third radiologist, with six years of experience in gastrointestinal radiology, who was not involved in the qualitative image analysis.

Quantitative analysis in axial images included: measurement of maximum anteroposterior diameter of the gland (pancreatic thickness) evaluated in pancreatic head (at the level of the portosplenic confluence), body (gland portion with maximum anteroposterior diameter to the left of the superior mesenteric artery) and tail (about 1 cm proximal to the distal end of the pancreas).

In the quantitative analysis measurement of pancreatic density using freehand ROI (region of interest drawn manually in order to include most of the pancreatic gland) in 6 and 64 slice axial images placed over the head (at the level of the portosplenic confluence), body (gland portion with maximum anteroposterior diameter to the left of the
superior mesenteric artery), tail (about 1 cm proximal to the distal end of the pancreas) was evaluated. We considered the mean value of all measurements (head, body and tail) for each individual patient and the mean value of all Patients of each two groups (NNAP and AIP).

Pancreatic density was also measured in 64-MDCT multiplanar curved reconstruction images using freehand ROI which included the entire pancreatic gland.

Vascularization behaviour in the different dynamic MDCT study phases (pancreatic, venous and delayed phase) was assessed for the two groups considering the rate of relative variation in enhancement from previous phase.

The ad-hoc parameter, Relative Enhancement Rate (RER) was defined by the following formula:

\[ \text{RER}_i = \left[ \frac{(D_i - D_{i-1})}{D_i} \right] \frac{1}{#t} \times 100 \]

where:

- \( \text{RER}_i \) = Enhancement Rate for Phase \( i \)
- \( i \) = phase number: (0= precontrast enhanced, 1= pancreatic, 2= portal venous and 3= delayed enhanced phases)
- \( D_i \) = mean pancreatic parenchyma density in phase \( i \)
- \( D_{i-1} \) = mean pancreatic parenchyma density in phase previous to \( i \)
- \( #t \) = the time elapsed between \( i^{th} \) and \( i-1^{th} \) phases

RER\( _i \) = relative enhancement rate for \( i^{th} \) phase; defined for \( i=1 \) to 3.

All densities were measured in Hounsfield Units (HU) and time in seconds. Mean pancreatic parenchyma density \( (D_i) \) was calculated as the mean of the three pancreatic segment mean densities (\( \frac{\text{mean}_{\text{head}} + \text{mean}_{\text{body}} + \text{mean}_{\text{tail}}}{3} \)) averaged over all patients of the same disease group.

In other words, the Relative Enhancement Rate of any phase is simply the relative change in parenchyma HU from that of the previous phase divided by the time elapsed since the last phase and represented as a percentage.

**Statistical analysis**
Distribution of continuous variables is reported as mean an standard deviation, whereas median and range (minimum; maximum values) when skewed distributed. Categorical variables are presented as numbers and percentages.

The inter-observer variability was assessed in determining qualitative and quantitative parameters of pancreatic parenchyma and vascularization, according to the k-statistics. The strength of agreement was assessed as follows: <0.20 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, 0.81-1.0 excellent agreement.

The comparison between subgroups, identified by pancreatic disease (NNAP, DAIP), was carried out using Student's t test, or Mann-Whitney U test (when skewed distributed), for continuous variables. Qualitative data were compared by the Chi square test or Fischer exact test when necessary.

P values were considered significant when less than or equal to 0.05.
Results

Qualitative Images Analysis

Pancreatic parenchyma showed diffuse enlargement in 14/14 (100%) of the DAIP cases (Fig. 1A) and in 18/22 (81.8%) of the NNAP cases (Fig. 1D) (p=n.s.). Swelling was present in 14/14 (100%) of the DAIP cases (Fig. 1 A-C) and in 2/22 (9.1%) of the NNAP cases (p<0.0001).

The main pancreatic duct dilatation was visible in 3/14 (21.4%) of patients affect by DAIP and in 2/22 (9.1%) of patients affect by NNAP, (p=n.s.). In all patients with DAIP the dilatation was diffuse.

When compared with parenchyma spleen in precontrast enhanced phase pancreatic parenchyma was isodense in all patients: 14/14 (100%) of DAIP patients and 22/22 (100%) of NNAP patients (p=n.s.).

When compared with the spleen parenchyma during the pancreatic phase of the dynamic study, the pancreatic parenchyma of DAIP patients appeared hypodense in 13/14 cases (92.9%: Fig. 1A-C; 2A-B; 4E), isodense in 1/14 cases (7.1%) and hyperdense in 0/14 cases (0%). In contrast, in the NNAP patients during the pancreatic phase pancreatic parenchyma appeared hypodense in 2/22 cases (9.1%), isodense in 20/22 cases (90.9%: Fig. 1D-F; 3A-B; 4A), and hyperdense in 0/22 cases (0%) (p<0.05).

When compared with the previous phase, pancreatic parenchyma during the portal venous phase appeared hypodense in 1/14 (7.1%), isodense in 2/14 (14.2%) and hyperdense in 11/14 (78.7%: Fig. 2C-D) of patients affected by DAIP. In patients affect by NNAP the pancreatic parenchyma appeared hypodense in 16/22 (72.7%: Fig. 3C-D), isodense in 6/22 (27.3%) and hyperdense in 0/22 (0%) (p<0.05). At last, in the delayed phase of dynamic study all DAIP patients (14/14: 100%: Fig. 2E-F) showed a retention of contrast media while all NNAP patients (22/22: 100%) showed (Fig. 3E-F) a wash-out (p<0.0001).

Stranding of peripancreatic fat was present in 13/22 (59.1%) of NNAP patients (Fig. 1F; 3; 4A-B). It was absent in all patient affect by DAIP (p=0.001).

Retroperitoneal fluid film was found in 15/22 (68.2%) of NNAP patients (Fig. 1E; 4C-D) and in none of the DAIP patients (p<0.0001).

Peripheral rim enhancement was seen in 3/14 (21.4%) of DAIP (Fig. 4E-F), but in none of the NNAP patients (p=n.s.).

Pleural effusion was found in 1/14 (7.1%) of DAIP and in 11/22 (50%) of NNAP patients (p<0.05).
Quantitative images analysis

The mean thickness of pancreatic gland evaluated in axial images was 37.5 mm, 32.1 mm and 26.8 mm respectively in the head, body, and tail of the gland of the DAIP patients (Fig. 1B-C). In NNAP patients (Fig. 1E-F), the pancreatic thickness was 33.1 mm, 25.8 mm and 22.8 mm respectively in the head, body and tail of the gland.

The mean pancreatic density evaluated in axial images at the level of head, body, tail and in 64 MDCT curved multiplanar reconstruction images are reported in table 1. During the unenhanced phase, pancreatic density value (Tab.1) is statistically significantly lower in NNAP then in DAIP patients (p=0.031). There is no difference between the two groups of patients during the pancreatic phase (p=0.10) while there is statistically significant difference (Fig. 5) during the portal (p=0.002) and the delayed venous phases (p<0.0001). No statistically significant difference was observed between the three different pancreatic segments (head, body, tail) regarding the measured density in all of the phases.

Density values observed in MPR images confirmed this.

The Relative Enhancement Rate (Fig. 6) from unenhanced to pancreatic phase (RER1) was greater in NNAP then in DAIP patients (density variation from 29.0 to 89.3 HU; RER1 = 12.84%/sec for NNAP vs. density variation from 37.7 to 72.0 HU; RER1 = 5.4%/sec for DAIP; p=0.0002). Passing from pancreatic phase to portal venous phase the Relative Enhancement Rate (RER2) remains positive in DAIP patients (density variation from 77.2 to 95.7 HU; RER2 = 0.65%/sec) while a progressive wash-out begins in NNAP patients (density variation from 89.3 to 78.7; RER2 = -0.22%/sec) (p<0.0001).

The Relative Enhancement Rate from the portal to the delayed venous phase (RER3) remains positive in DAIP patients (density variation from 95.7 to 112.1 HU; RER3 = 0.14%/sec) and negative in NNAP patients (density variation from 78.7 to 64.0 HU; RER3 = -0.16%/sec) (p<0.0001).
Fig. 0: Figures 1A-F. DIFFUSE AUTOIMMUNE PANCREATITIS (DAIP: A-C); NON NECROTIZING ACUTE PANCREATITIS (NNAP: D-F). PANCREATIC ENLARGEMENT AND GLANDULAR SWELLING. 64 MDCT pancreatic enhanced phase multiplanar curved reconstruction (A,D) and axial (B-C; E-F) images. In both disease diffuse pancreatic enlargement is present (A,D). Thickness measurement of pancreatic gland evaluated in axial images in the head (maximum anteroposterior diameter at the level of portosplenic confluence: B,E) and in the body and tail (maximum anteroposterior diameter at the level of gland portion to the left of the superior mesenteric artery and 1 cm proximal to the end of the pancreas: C,F) show increased value compared to pancreatic normal value. Curved multiplanar reconstruction and axial images show diffuse loss of...
glandular lobularity (pancreatic swelling) in DAIP (A-C). Retroperitoneal fluid film (E: arrow) and pancreatic stranding (D,F: short arrows) are present in NNAP patients. In DAIP (A-C) stent of common bile duct (arrowheads) and enteral tube (black arrow) are present.

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Fig. 0: Figures 2A-F. DIFFUSE AUTOIMMUNE PANCREATITIS (DAIP). PANCREATIC DENSITY. 64 MDCT axial (A,C,E) and curved multiplanar reconstruction (B,D,F) images during pancreatic (A-B), portal venous (C-D) and delayed (E-F) enhanced phases. When compared with the spleen during pancreatic phase of dynamic study pancreatic parenchyma results hypodense (A-B) likely because of lymphoplasmacytic infiltrate and fibrosis. When compared with the previous phase parenchyma during the portal venous
phase becomes more dense (C-D). During delayed phase of dynamic study it shows retention of contrast media (E-F). Pancreatic density evaluation with freehand ROI in 64 MDCT curved multiplanar reconstruction images (B,D,F) confirms these data. Main pancreatic duct is narrowing, not visible. Stent of common bile duct (arrow) and enteral tube (arrowhead) are present.

Fig. 0: Figures 3 A-F. NON NECROTIZING ACUTE PANCREATITIS (NNAP). PANCREATIC DENSITY. 64 MDCT axial (A,C,E) and curved multiplanar reconstruction (B,D,F) images during pancreatic (A-B), portal venous (C-D) and delayed (E-F) enhanced phases. When compared with the spleen during pancreatic phase of dynamic study performed 72 hours after clinical onset parenchyma result isodense (A-B) because
of interstitial edema without necrosis. When compared with the previous phase, parenchyma during portal venous phase becomes hypodense (C-D). During delayed phase of dynamic study it shows wash-out (E-F). Pancreatic density evaluation with freehand ROI in 64 MDCT multiplanar reconstruction images (B,D,F) confirms these data. Thin peripancreatic halo hypodense in all phases of MDCT examination (arrows) due to mild inflammatory changes of fat surrounding the pancreas (peripancreatic stranding) is visible. Bile ducts dilatation is not present.

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Fig. 0: Figures 4A-F. NON NECROTIZING ACUTE PANCREATITIS (NNAP: A-D); DIFFUSE AUTOIMMUNE PANCREATITIS (DAIP: E-F). PANCREATIC STRANDING (A-B); RETROPERITONEAL FLUID FILM (C-D); PANCREATIC ENHANCEMENT RIM
(E-F). 64 MDCT axial images during pancreatic (A,C,D,E) and delayed phase (B,F). Peripancreatic halo (A,B: arrowheads), hypodense in pancreatic (A) and delayed (B) phases of MDCT dynamic study, represented by streaking of peripancreatic fat due to inflammatory changes and edema, is present in NNAP (peripancreatic stranding). NNAP shows thickening of left anterior pararenal fascial plane (C-D: short arrows) due to retroperitoneal inflammation and edema (retroperitoneal fluid film). In DAIP peripheral halo of contrast enhancement (E-F: arrows), hypodense during pancreatic phase (E), hyperdense in delayed phase (F) compared to pancreatic parenchyma due to chronic inflammatory changes of peripancreatic fat may be present. Left kidney shows cortical focal area (curved arrow) of reduced enhancement in pancreatic (E) and delayed (F) phases, due to chronic autoimmune pielonephritis associated to autoimmune pancreatitis (histological diagnoses).

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**Fig. 0:** Figure 5 PANCREATIC DENSITY VALUES IN ALL PHASES OF MDCT STUDY IN DAIP AND NNAP PATIENTS. The graph shows the values of mean measurement of density expressed in HU of the pancreas (head, body and tail) for each individual patient during pancreatic, portal venous and delayed phases (respectively 20, 60 and 180 seconds after bolus tracking begun) in DAIP (black curve) and NNAP (gray curve). In NNAP patients the highest density value is reached faster during pancreatic phase with a wash out in successive portal and delayed phases. In DAIP Patients the density values increase slowly, albeit plateauing, during pancreatic and portal venous phases, reaching the highest value in the delayed phase.
Fig. 0: Figure 6 RELATIVE ENHANCEMENT RATE (RER) OF THE PANCREAS IN DAIP AND NNAP. The graph shows the values of Relative Enhancement Rate (RER) across all MDCT phases. RER1 (referring to the passage from pre-contrast to pancreatic phase) resulted positive in both disease but much higher in NNAP than in DAIP. RER2 (referring to the passage from the pancreatic to the portal venous phase) was positive for DAIP cases while negative for NNAP cases reflecting the increasing, albeit plateauing, enhancement in pancreatic parenchyma between the pancreatic and venous phases in DAIP and the wash-out characteristic of this same interval in the NNAP. The same pancreatic enhancement behaviour was maintained during the passage from portal to delayed venous phase (RER3).
Conclusion

Contrast agent enhanced MDCT imaging is a useful technique for differentiating DAIP from NNAP at clinical onset. Contrast enhancement pattern, particularly by considering the Relative Enhancement Rate parameters presented in this work, provide qualitative and quantitative clues to the differentiation of diseases. The retroperitoneal findings of peripancreatic stranding and retroperitoneal fluid film, characteristic of NNAP, and late-phase peripheral rim enhancement, characteristic of DAIP, can also assist in the differential diagnoses of two diseases.
References


